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TRANSACTIONS OF THE
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VOL. X. DECEMBER 1, 1915. NO. 1

THE PEDAGOGICS OF PATHOLOGY

PRESIDENT'S ADDRESS

JOHN M. DODSON

The medical profession of Chicago is justly proud of the Pathological Society. In the opinion of many it has been doing, for some years, the most consistent and the most significant work of any of our local medical organizations. Its programs have contained some noteworthy contributions to the literature of pathology; its meetings have afforded an important stimulus, not only to the men engaged in the pursuit of pure pathology, but to those employed in other branches of medicine; they have furnished a convenient forum for the exchange of ideas and information between the representatives of the several special branches of medicine, and last, but not least, by inviting undergraduate students to attend and to contribute to its discussions, this Society has been one of the most effective agencies in encouraging these students, at the threshold of their medical lives, to pursue those methods of accurate, painstaking observation, and to record and present the results of their observation in the manner which we designate as research. I know of no more effective, educational method than this, and it is certain that the opportunity, which these young men and women have here enjoyed has had, and will continue to have, a profound and beneficent influence on their future careers.

To preside for a period over the deliberations of such a society, is a grateful task, and to be chosen for such an office an honor keenly appreciated.

At first thought it might seem that the President of this Society should always be a recognized pathologist —one who is devoting himself exclusively to that branch of medical science, but in electing to this office, as the Society has done on several occasions, men who are engaged in other lines of medical work, it has recognized the peculiar position of pathology as the most important connecting link between the fundamental medical sciences on the one hand, and the applied or clinical branches on the other.

I can lay no claim to the office with which you have honored me by reason of any contributions to pathology, nor even, I regret to say, by any considerable participation in its discussions. I have had, however, a very deep interest and pride in its work, dating from its first beginning as a *real* pathological society.

Joining it shortly after I came to Chicago in 1889, I found it to be a local medical society, its membership made up of physicians living on the West Side of the city, and its discussions having to do with all sorts and phases of medical topics of interest to the general practitioner. Its meetings were held wherever a convenient and inexpensive (preferably a *free*) meeting place could be had, at the offices or homes of its members, in college or churches. The first meeting which I attended, as I recall, was in the library of the Congregational Theological Seminary at the corner of Ashland and Warren Avenues. Possibly the baptism which the Society thus received from the drippings of the adjacent sanctuary, may account for the pious, not to say sanctimonious, demeanor and conversation of some of its members as I hear it from time to time exemplified on the golf links.

Becoming the Secretary of the Society not long after becoming a member, and having charge at that time of the laboratory for physiology at Rush Medical College, a room well adapted for the meetings of the Society and conveniently located, arrangements were made, through the courtesy of the faculty of Rush, to

hold the meetings in that room, and here it came to the attention of Drs. Hektoen, Weaver and Le Count and others of the Department of Pathology and Bacteriology, who saw in it the possibilities of a scientific society for which the conditions were just then ripe. And they proceeded to make of it in fact—as it was already in name—a pathological society. How much of its subsequent success is due to their untiring efforts and especially to the faithful, efficient service of our secretary for life is known to all. To our appreciation of his service we sought to give expression last year.

In conformity with the established precedent that the presiding officer shall be holden for some remarks in inaugurating his term of service, I venture to present some reflection on the "Pedagogics of Pathology." As members of this Society, and of the medical profession we are all interested in the question of medical education, whether engaged or not in actual teaching. In the curriculum of the medical school, pathology occupies a position of especial interest and importance in relation to the other branches. More than any other topic it bridges the gap which at the present time exists between the sciences fundamental to medicine, and the clinical subjects.

Pedagogics—the science of teaching methods—has been making rapid progress in the last half century, and has come to occupy a place among the recognized sciences.

Modern pedagogy is of necessity a recent growth, because experimental psychology itself, upon which it is based, is barely 40 years old. The first laboratory for experimental psychology was established by Wendt in Leipsic about 1876, while in this country no such laboratory existed until the one opened by Dr. G. Stanley Hall, at the Johns Hopkins University in about 1888. Previous to this time, however, important contributions had been made to the teaching art, and the ideas of Pestatalozzi, of Hebart, of Rousseau and others were gradually influencing our educational methods. The importance of laboratory or objective methods, teaching by closer attention to the individual pupil, and the splitting of large classes into smaller

and smaller groups, the elective plan, the continuous session, best exemplified in the quarter system, research as an essential function of the university and a pedagogic method, the division of the sciences into smaller subdivisions, specialization in a word—these and other pedagogic innovations were and still are receiving attention from educators, and are being adopted throughout our educational system from the kindergarten onward. Of special importance were the introduction of objective methods of teaching in field and laboratory, in the recognition of the individual differences of pupils, and the consequent necessity of adjusting the educational process to these differences by some scheme of election or selection of topic, method and teacher in order to secure the best results.

Laboratory methods began to be introduced into the American colleges, on any considerable scale, not much more than half a century ago, at first in chemistry, then in physics, and later in the several biologic branches. The supplanting or supplementing of the older didactic methods of lecture and recitation by these laboratory exercises extended rather rapidly in the literary college, but they made their way much more slowly in the medical school. It might have been expected that the contrary would have been the case when it is recalled that for a century or more one laboratory or practical course—that of human dissection—had occupied a recognized place in the medical curriculum, and was required of every student, but it is barely thirty years since any other laboratory course was generally required in the medical college. It is but little over thirty years since the writer attended the two five-month courses of lectures at that time required for graduation in Rush Medical College. Coming from a small university, where even at that time the laboratory exercise constituted the most important feature of instruction in all of the sciences, it seemed strange to find no practical work whatever, aside from dissection and a brief four or five weeks' superficial course in chemistry. A year later, having discovered that he was inadequately prepared, it was decided that he should take another course of lectures, and the choice

of Jefferson Medical College was determined by the fact that it alone, of all of the medical colleges in this country, offered a practical or laboratory course in connection with each of the seven departments—chairs, as they were called—which made up the medical college of that day, namely, anatomy, physiology, chemistry, materia medica, medicine, surgery and obstetrics. Most of these practical courses were brief and superficial, consisting in large part of demonstrations by the teacher rather than of individual work by the student, but they were the beginning of better things.

The explanation of the tardy adoption by the medical faculty of these modern methods is to be found in the fact that its members were not primarily educators, and they were therefore not keeping closely in touch with the advances in pedagogic methods. They were for the most part, even in the fundamental branches, practitioners of medicine for whom the giving of medical lectures two to four times a week during the five or six winter months was an incidental avocation. Not until the medical schools came to have a real vital connection with the university and its faculty was brought in close contact with and came in part to be composed of men who were making teaching their chief if not the sole business of their lives, was any considerable progress made in the introduction of more rational and effective methods.

Pathology in my student days was not recognized as an essential subject in the medical curriculum. Indeed at Rush it was not only not taught but was ridiculed by some of the most influential members of the faculty, as "Dead House Medicine." In Jefferson Medical College, perhaps at that time the most progressive medical college in this country, a few incidental exercises by a subordinate teacher, who presented some postmortem specimens to the class, comprised all that was offered. How great has been the advance in the subsequent quarter century is in no wise better illustrated than the number and character of the contributions made by undergraduate students to the transactions of this society.

Pathology has been extending its scope very rapidly. The term pathology no longer stands for mere pathological anatomy, the study of the end-results of disease, but has come to signify, as its etymology implies, a comprehensive study of the phenomena of disease in the living, the behavior of cells, tissue, organs and systems in an abnormal environment, or their reaction to abnormal stimuli — an exhaustive search for the causes of these abnormalities — physical, chemical and biologic, and rationale of the processes by which these etiologic factors bring about the phenomena which we call disease. Indeed, some of the more recent textbooks on medicine include, under the heading of pathology, pathogenesis and pathologic anatomy everything, in short, but diagnosis, prognosis and therapy.

The methods by which this comprehensive knowledge is sought are more and more becoming the methods of exact, carefully controlled experiment on animals. The mere study of postmortem changes, important though it is, comes yearly to occupy a relatively less important rôle in the task of the pathologist. Infection and immunity, serology, protozoölogy, chemical pathology, these and other phases of the subject newly born in the last decade or two, are rapidly changing our whole conception of pathology, are greatly enlarging its scope, and are, as it seems to me, necessitating a constant readjustment of the methods of instruction by which the coming generation of practitioners must be educated in pathology.

The pedagogics of pathology involves a consideration of (1) its relative importance in the curriculum, that is, the number of scheduled hours, that should be assigned to the subject; (2) its proper sequence in the program of courses to be determined by the prerequisites which are essential for its intelligent study, and by its relation to the more advanced clinical subjects for the pursuit of which some knowledge of pathology is necessary; and (3) the methods to be employed in the teaching of the subject, and this depends largely on one's conception of the scope and content of pathology as a science.

A survey of the curricula of about forty of the leading university medical schools of the United States discovers the fact that while there are considerable variations in the courses in pathology offered in these schools, as to the three points just mentioned, on the whole the differences are less marked than are those in the clinical subjects.

The amount of time assigned to the subject is somewhat difficult to determine, as some of the topics, taught in most schools under pathology, are offered in others in connection with bacteriology, while other topics, for example, laboratory or clinical diagnosis, are taught in the department of medicine or in other clinical departments. As nearly as can be estimated the time assigned to pathology ranges from 210 hours in one school to a maximum of 504 hours in the University of Ohio.

One of the most conclusive evidences that up to eight or ten years ago the principles of pedagogy were little understood or regarded by medical faculties, was the great diversity in the number of hours assigned to the several medical branches. You will recall the rather startling findings of the investigations made as to this matter a decade ago by the secretary of the Michigan State Board of Medical Examiners, the president of the Illinois State Board of Health, and by the Council on Medical Education of the American Medical Association. It was found that the number of scheduled hours assigned to some of the important medical subjects varied by as much as 300 or 400 per cent., and that some of the minor subjects, for example, orthopedic surgery, occupied as much of the student's time in some colleges as a major branch like medicine or general surgery.

It is obvious that these curricula were not prepared with any logical consideration of the relative values of the medical branches. Each instructor, impressed with the magnitude of his own subject, clamored for more and more time, insisting that he could not "cover the ground" of his branch of medicine in any number of hours that could in reason be given over to it in a four-year course of study. The construction of a

medical curriculum from the point of view of the average student's working capacity and the logical division of his total working hours between the several branches in ratio to their relative importance to the medical practitioner seems not to have been attempted until a very recent period.

When the problem is approached from this standpoint it becomes at once evident that by no possible scheme can such a number of scheduled hours be allotted to any branch as will make it possible for the instructors to completely "cover the ground" of that branch. The task of each department is to make such use of the number of hours assigned to it, by faculty vote, as will secure to each student the largest possible educational result for the expenditure of that time in the given topic. With a curriculum blocked out on such a basis, pathology cannot logically demand more than 8 or 9 per cent., together with bacteriology not to exceed 12 per cent. of the total number of scheduled hours in the four-year course of study, and as this total in the average medical school is approximately 4,400 hours, the time assigned to pathology should not exceed 350 or 400 hours.

I find that the average allotment to the courses in pathology in the curricula of the forty colleges which I have examined is about 350 hours, although there are some marked exceptions. The time allotted to bacteriology ranges from about 100 to 200 hours, with an average of 150, thus making a total for the two subjects fairly proportionate to their importance in relation to the other branches of the medical curriculum.

The logical sequence of the medical subjects is determined by certain fundamental pedagogic principles.

The study of structure logically precedes the study of function; knowledge of the normal is essential to an understanding of the abnormal, altho the study of the latter often yields valuable information about the normal; a broad knowledge of the principles, facts and methods of any growing science, as are those fundamental to medicine, is an essential prerequisite if the student is to be so grounded in that science as to be able to keep abreast with its progress after his student

days. It is a fatal error to present the fundamental medical sciences with too exclusive reference to their practical application to medicine and surgery, although the occasional illustration of the bearing of anatomy, physiology, pathology, etc., on their practical application to clinical medicine is of distinct advantage. With these principles in mind the position of pathology in the medical curriculum is not difficult to determine. There is a rather striking uniformity in the place assigned to bacteriology and pathology in the courses of study in the several colleges. In the majority of colleges bacteriology is offered in the first semester of the second year, followed by general pathology in the second semester, and by special pathology, with autopsies in the third year. In a few institutions bacteriology is given in the first year, and in two instances pathology proper is begun at this time. In a number of colleges advanced pathology with autopsies and special topics such as surgical, gynecologic, neurologic and dermatologic pathology are continued into the senior year.

Bacteriology, it seems to me, might, with advantage be divided into two parts, general bacteriology with laboratory technic, being given in the first year, or better still, required for admission, to be followed by a briefer course in the pathogenic bacteria, and in infection and immunity, in the second year, preferably the first semester. The fundamental course is an excellent one for the beginning student, no work in the other sciences being prerequisite to the intelligent study of the subject, and the laboratory technic affording a good training for the laboratory exercises in the other branches. It seems impracticable to crowd such a course into the two years of premedical work at present demanded by most schools, but it is probable that this minimum amount can, before long, be extended to three years, and thus provide time for bacteriology.

The position of general pathology in most curricula is as it should be. It secures to the student the necessary preparation in anatomy, gross and microscopic, embryology, physiology, biologic chemistry and bacteriology, and, on the other hand, links these subjects closely to the clinical subjects. I would urge, how-

ever, the importance of placing pathologic anatomy with autopsies later than is now done in many schools. The student should have acquired some considerable first-hand knowledge of the phenomena of disease in the living patient before he studies the final outcome of serious disease as disclosed at the autopsy, and as often as possible he should follow the individual patient, dying from some affection which he had observed in life, to the postmortem table. Of especial educational value is the study of a few cases, seen at autopsy, exhaustively by every feasible method of examination, as contrasted with a second-hand survey of the whole field of pathologic anatomy by lecture, textbook and recitation. One of our members not long since described his own method of conducting such a course, which seems to me in every way admirable.

May I, in this connection, comment on the singular and widely prevalent perversity with which teachers in all lines and grades of education in this country are prone to get away in their practice from the fundamental idea and purpose of education?

Its primary purpose is to develop the mental faculties, *not* to impart information. And this is quite as true of medical as of any other kind of education. That the pupil shall be educated, trained to observe accurately and thoroughly, to record his observations clearly and concisely, and to reason logically from his findings to sound deductions—*that* is the main purpose and function of any educational process, be it medical, pathologic or any other. We in America seem especially obtuse in our failure to recognize this vital truth, as is shown conspicuously in the character of our examinations. We have made some progress in our teaching methods, though we have yet much to learn, but we continue to test the results of our work by methods a half century out of date. In examinations for graduation, for licensure to practice (with exceptions now in a few states) and in competitive examinations for internships in the best hospitals, the papers set, are wholly written papers of such sort as to test only the volume of facts which the candidate has been able to cram into his cranium—a test, in other words,

of but one mental faculty, the memory, and that by no means the most important. Into the student's real power to see and hear and feel things, to know *what* he observes, and to draw sound conclusions from findings; in short, his ability to *do* the things he is to be called upon to do as an intern and a practitioner of medicine, we make no inquiry whatever. If we are to give our students the proper conception of what they are attending the medical school for, and an effective stimulus to really develop all of their mental faculties, along medical lines, we must radically change the character of our examinations.

The teachers of pathology are in an especially advantageous position to set an example in this regard, and to exert a profound influence for the betterment of our methods of examination.

Another serious mistake is the growing tendency to crowd some clinical subjects into the sophomore year. In the University of California, for example, courses in medicine, surgery, obstetrics, ophthalmology and dermatology now occupy a considerable portion of the time of the second semester of the sophomore year; at Johns Hopkins the sophomores take medicine, both clinical and didactic, surgery and pediatrics; at Harvard, medicine, surgery, obstetrics and dermatology occupy ten hours weekly of the twenty-five or thirty available, while in Cornell medicine, surgery and obstetrics are begun at this time. The time available for the fundamental sciences of anatomy, general pathology, etc., is all too short when the full time of the two years is devoted exclusively to them. The education which the student is obtaining in these fundamental subjects in these two years is the only systematic instruction he will ever get in those branches and must serve him for a lifetime. Most students leave the medical college at graduation with a resolve to review these branches from time to time, but very few ever do so. Deficiencies in clinical training are readily amended, because these subjects are right in line with the physician's daily work, shortcomings in the fundamental branches can be corrected only at a considerable sacrifice of time, money and energy.

I have indicated that I would lay much less stress on pathologic anatomy than has been and still continues to be the custom in most schools, and more, increasingly more, time on experimental pathology, chemical pathology, serology and the other newer developments of the subject. As to pathologic anatomy much can be done to familiarize students with the gross and microscopic appearance of diseased tissues and organs (and this with the minimum expenditure of effort by both student and teacher) by having displayed in a well-lighted central place, frequented by the student body for study or lounging, pathologic specimens, plates, drawings, charts and other illustrative materials. In idle moments one can accumulate a large amount of information by this means. It is the height of stupidity to lock up material of this sort in dark inaccessible cases to be brought forth only on special occasions.

There is need in most schools of a better correlation between the department of pathology and the clinical departments. The clinical teachers are, for the most part, busy practitioners having little time, even when they have inclination, to keep in touch with what is going on in the pathological department so as to command the resources of its museum in their clinical teaching. The instructors in pathology can accomplish a great deal to secure more thorough and accurate presentation of the pathologic side of the clinical subjects if they are constantly calling to the attention of the clinicians to the materials in their museums and laboratories, and are themselves available at convenient hours to respond to a summons to the medical, surgical or other clinic to demonstrate pathologic specimens, illustrative of the topic being presented or of the clinical patient who is being shown, and to explain the newer, more refined laboratory methods of diagnosis.

No colleague of mine would think it possible for me to get through a discussion on such a subject without allusion to the elective system. I should be sorry to disappoint anyone or to lose such an opportunity. May I say then first that after fifteen years of experience

and observation I am more confirmed in my belief than ever before of its applicability to and its advantage with suitable restrictions in medical education. The elective principle has been adopted and is in operation in one form or another in every college and university of any importance in this country. It has been an integral part of the educational system in the German and most other foreign universities, in the medical as well as in other departments, for over fifty years. I have elsewhere described the plan and discussed its advantages in the medical curriculum at length, and do not here purpose to review that discussion. However, to correct certain erroneous impressions, which seem to be quite prevalent, I may say that the elective system, properly administered, does *not* mean the unrestricted freedom of the student to do just as he pleases—to choose any course of study which strikes his fancy. Its chief advantages do *not* lie in the choice of branches or even of topics, but much more in the choice of methods of study—by lecture, recitation, laboratory, clinic, research—and of the instructor under whom each course is to be pursued. Its purpose in the medical school is *not,* or should not be, to encourage or even to permit the undergraduate student to follow a restricted course of study in preparation for a special line of practice, although in this form it is in operation, mistakenly as I believe, in two or three of our leading medical schools. It does *not* mean, for example, that any student should be permitted to neglect pathology or medicine or any special clinical subject. It *does* make for his opportunity to get the minimum amount of that subject by the method and under the instructor that will insure for him the best training, that is, the maximum educational gain, in that branch of study, and it should permit and encourage him to pursue that subject much beyond the minimum amount required for graduation if he finds therein, as very many students do, the best medium for developing his powers of observation and reasoning.

As surely as individuals differ, as they do differ widely, in mental equipment and capacity, just so surely

can we obtain the best results in education only by such elasticity in our methods as makes possible the adjustment of the educational procedure to each student's capacity, peculiarities and needs.

And finally, I would speak for a much wider adoption and extension of the method of research in medical education. The daily practice of medicine for which we are preparing most of our pupils is research of the highest order and the most difficult type. We train the neuromuscular apparatus and the special senses to efficiency in any particular direction, by their constant exercise in that direction. How can we better train the mental faculties for research at the bedside than by their exercise in research, in laboratory and clinic? No one would deny that a certain body of fundamental facts and principles must be memorized by every medical student, and facility in certain technical procedures ought to be acquired, but if we hope to arouse in the student a real enthusiasm for his work and to develop his power of independent initiative and accomplishment in the setting and the solving of problems, it can be done only—certainly most effectively—by setting him to the task of solving problems within his capacity, involving factors within his control, his work being carried on under intelligent, wise supervision. The problems of pathology are peculiarly well adapted for this purpose. They may be so selected as to have to do with materials and factors within the scope of the student's ability and training, and they are of interest to him because he can readily see their bearing on clinical medicine for which he feels he is fitting himself. If he is to have zeal in their pursuit, however, they must not be the threshing over of old straw, but new problems whose solution he feels may constitute a real contribution, however small, to medical science. If he can then present the results of his efforts to a dignified, earnest group of his elders, such as assemble at the meetings of this Society, it means for him a generation of enthusiasm, a development of real power, such as no other educational method can produce.

This Society has great reason to be proud of the subsequent work of many men and women who found here their first opportunity and their best inspiration. It is certain to have increasing cause for gratification, as the years go on, in the results of this phase of its activities.

Our efficient Secretary so admirably looks after the affairs of this organization that the President has little to do but to sit in the chair and look pleasant. This I pledge you to do to the best of my ability, and with the Secretary to run the machine I feel confident that we may look forward to a year of interesting and profitable work.

Oct. 11, 1915.

RECENT STUDIES OF THE STRUCTURAL CHANGES IN MENTAL DISEASES

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Newer methods of staining have led to the establishment of more definite groups of changes in mental diseases. New types of reaction have been found and certain pathological entities have been described.

Alzheimer and Nissl have described the changes in paresis in a masterly manner. Briefly outlined, we find in the pia mater increased fibrous tissue, a glial overgrowth, with constant infiltration of the thickened areas by plasma cells, giant cells, mast cells, lymphocytes and Abräumzellen. The blood vessels show obliterating endarteritis, thickening and degeneration of the muscularis, new vessel formation and perivascular infiltration with plasma cells, mast cells, lymphocytes and degenerative products.

The occurrence of plasma cells in profusion is more or less pathognomonic of paresis, occurring in few other conditions, in like manner (cerebral lues, trypanosomiasis and malaria). Stäbchenzellen, attributed by Alzheimer to originate from the adventitial cells, are constantly found, most frequently in the superficial

layers, running parallel to the incoming blood vessels. They assume various forms, from that of a needle to that of a link of sausage. Amyloid and colloid bodies, mast cells and a few Abräumzellen and Gitter cells are found in various places.

The ganglion cells show all the forms of degeneration which have been described by Nissl. A constant change is seen in their fibrillary structure, consisting of disintegration of the neurofibrillae, agglutination, paucity of cell process, diffusely stained bodies, fragmentation and localized swelling and beading of cell processes. The architecture of the cortex is constantly disturbed. There is a diffuse degeneration of the nerve fibers, especially the tangential fibers of the superficial layer of the cortex. The glia fibers are thickened and numerous spider cells are present. Giant astrocytes are common. Satellitosis is constant and the blood vessels are surrounded by clinging glia cells.

The microscopic anatomy of pellagra presents a number of interesting pictures. The glia cells and nuclei show various forms of degeneration. Astrocytosis, while common, is not present to the degree met with in paresis or senile dementia. The cell processes of the astrocytes are thickened and their bodies frequently undergo a granular degeneration. The processes of these cells, in many instances, are bent and twisted and their insertion feet by which they are attached to the blood vessels, thickened. A cystic degeneration of nonfatty character is found, similar to that described by Cerletti in cases of pernicious malaria; ameboid glia cells described by Alzheimer as occurring only in recent and active diseases of the brain are found here. The ganglion cells show, in recent and acute cases, a characteristic change. Axonal reaction, produced experimentally by Marinesco and Van Gehuchten, resulting from an injury to the neuron at a distance from the cell, is constant and widespread. The cell is swollen and rounded and the nucleus displaced to the periphery. The tigroid substance has for the most part disappeared from the central portion of the cell, blocks staining well being often left around the periphery and especially in the base of the larger dentrites. This

reaction involves specially the Betz cells and those of Clarke's column. The picture is identical with that described by Meyer under the title of central neuritis, and is a mode of reaction to some toxin which is not specific and which occurs in other conditions. Occlusion of the central canal in the cord, caused by a definite central gliosis, is almost constantly found. Pigmentary changes are marked in the ganglion cells and about the vessels. They consist of pigmentary deposits of fatty, fibrinoid, protognoid and basophilic granules. Scattered degeneration of the nerve fibers is found in the spinal cord, with an asystemic involvement of Goll's column, the crossed pyramidal and Lissauer's tracts.

The psychoses of senescence offer two interesting pictures. The Redlich-Fischer plaques, for a long time mistaken for artefacts, are found in all cases of senility, but extensively and to a marked degree in senile dementia. Their origin is still a mooted question. They are probably composed of a central area of necrosis and degenerative products surrounded by glia fibers.

Presenile delusional insanity is notable for the presence of Alzheimer's Basket cells, found chiefly in the hippocampal gyrus.

March 8, 1915.

RENAL LESIONS IN CHRONIC ANAPHYLAXIS

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(From the Pathological Laboratory of the University of Illinois, Chicago)

This report concerns the results of an attempt to produce kidney lesions by repeated anaphylactic shock in guinea-pigs. Beef serum and egg white were used as antigens. Sensitizing doses ranged from $\frac{1}{1000}$ c.c to 1 c.c. The interval between the sensitizing dose and the first toxic dose was usually about three weeks. The toxic doses ranged as high as 10 c.c., though the attempt was made to give the smallest dose that would produce in any given case a distinct shock. Some of the animals were under observation for longer than eight months,

but the average was about four months. Those animals that died acutely during anaphylaxis were posted at once. Others were killed at varying intervals up to eight weeks after the last injection. It is, of course, difficult to so regulate the dose of proteid as to give an animal repeated anaphylactic shock and still keep it alive. If the dose is too large, the animal dies; if the dose is too small no shock is produced, and the animal becomes refractory to anything but very large doses. Usually after a single large dose an animal would be refractory for several weeks. Three types of controls were used: normal animals; animals dying from a single shock (to show that the lesions produced were not the result of acute anaphylaxis); and animals receiving several (12 to 15) doses of proteid so spaced as to avoid anaphylaxis (to show that the lesions were not the result of the proteid injected, but of the shock produced).

The findings were based on the results of an examination of twenty-three guinea-pigs, including six controls, and are as follows:

Hyperemia was frequently present, especially in those dying of acute anaphylaxis and was most marked in the glomeruli. Hemorrhage was frequently present in those dying of acute anaphylaxis, but was never extensive. Degeneration, desquamation and necrosis of tubular epithelium. This change was seen in all cases and was usually quite prominent. It was seen especially in the proximal convoluted tubules, but also in the ascending limb of Henle's loop. In the earliest stages the cells are swollen and the margins frayed. Then vacuoles form at the bases of the cells and the nuclei become pyknotic. These vacuoles do not take the osmic acid stain. These vacuoles may increase in size till the cytoplasm resembles a badly torn network or becomes displaced toward the center of the tubule and the nuclei become fragmented or disappear. This was the stage most commonly observed. Desquamation was usually observed and regeneration frequently. Vacuolation was rather an acute process and was confined almost entirely to those cases dying of acute anaphylaxis, or killed soon after the last injection. If

killed three weeks or more after the last injection, vacuolation was less prominent or absent, and necrosis and desquamation more prominent.

Swelling and proliferation of capillary endothelium was observed in 70 per cent of cases. This is rather a late change, and with two exceptions occurred only in animals that had been under observation for three months or longer. In a few cases proliferation of the capsular epithelium of the glomeruli was observed. In one case there was fibrous thickening of the glomerular capsule.

Small areas of round celled infiltration were observed in nearly all cases. These were located in the cortex, and usually near blood vessels, and were usually quite numerous. Distinct scar formation was not seen in any case.

Oct. 11, 1915.

REPORT OF A CASE OF ACUTE LYMPHATIC LEUKEMIA

WITH EXCESSIVE ENLARGEMENT OF THE THYMUS

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(From the Memorial Institute for Infectious Diseases, Chicago)

A Hungarian boy, 5 years old, was brought to the hospital for diphtheria. The following history was obtained from the father: One month before admission patient had measles. At this time the cervical, axillary and inguinal lymph glands were about the size of peas. A few days after the measles the boy had an attack of what the father calls "croup" and was almost suffocated.

The physical examination revealed a pale, cyanotic, emaciated, rachitic boy, who appeared toxic. Breathing was labored, but not of the type due to laryngeal stenosis; as the cause appeared to be lower down. A purulent nasal discharge was present and no membrane visible in the throat. The teeth in poor condition. The anterior and posterior cervical, the submaxillary, the anterior and posterior auricular, the axillary, and inguinal glands were enlarged, from 0.5 to 2 cm. in diameter, the individual glands being discrete, firm, freely movable in relation to one another, and to the underlying and overlying tissues. Many large and small râles were heard in the lungs, which were otherwise negative. Per-

cussion revealed an area of dulness extending from the top of the sternum to within 2 inches of the lower end of the xyphoid process; laterally the dulness extended two fingers' breadth to each side of the sternum. This dulness was thought to be due to enlarged mediastinal glands and the dyspnea explained as due to pressure on the lower trachea and bronchi. The upper heart border, by percussion, appeared to be at the upper margin of the third rib; the left border about one finger's breadth beyond the nipple line; the apex in the fifth interspace. The heart sounds were not easily heard. The abdomen was tender and distended. The liver extended three fingers below the costal margin. The spleen was readily palpable, the lower end lacking 1 cm. of being on the same level as the umbilicus.

A large dose of antitoxin was given which soon controlled the diphtheria. Cultures taken from the tonsils contained diphtheria bacilli. A blood count revealed 370,000 white cells, 95 per cent. of which were lymphocytes of the small variety, slightly larger than an erythrocyte, 3 per cent. neutrophils and 2 per cent. transitional cells. A blood culture made on the second day after admission remained sterile. The urine contained an abundance of urates. The stools were almost black, but no blood could be detected.

The boy could not lie on his back. The breathing was much easier when propped up with several pillows, lying on either side for a few minutes, and at times relief was obtained by sitting upright.

On the fourth day after admission, there were 124,000 white cells, 87 per cent. lymphocytes, 7 per cent. neutrophils, 4 per cent. transitional cells and 2 per cent. large mononuclear cells. Hemoglobin, 35 per cent. On this day a few epithelial and granular casts appeared in the urine; urates decreased. On the fifth day there were 5,450,000 red cells, 150,000 white cells and 28 per cent. hemoglobin. Another blood culture was made and yielded an abundant pure growth of *Staphylococcus aureus*. On the sixth day there were 3,670,000 red cells and 155,600 white cells. The slightest exertion now would cause a marked increase of dyspnea. On the seventh day the boy died suddenly, five weeks after the apparent onset of the disease. The clinical diagnosis was acute lymphatic leukemia and diphtheria.

Autopsy.—All the superficial lymph glands were enlarged. The anterior portion of the chest was occupied by a thymic swelling measuring 18 by 12 by 9 cm. The margins of the lungs could just be seen on each side of the swelling. The apex of the heart could be seen below. The mass was firmly adherent by fibrous tissue to the sternum, intimately attached

by fibrous tissue to the pericardium and diaphragm, to the trachea, larger bronchi and the bases of the lungs. The mass was surrounded by a thick, firm, fibrous capsule. When sectioned a milk white fluid exuded from the cut surface which revealed several small hemorrhages into the substance of the mass. Microscopically, this tissue consisted of stroma and small lymphocytes; no Hassall's bodies were found. All the internal lymph glands were enlarged to from 0.5 to 2 cm., and when sectioned, exuded a milky white fluid, similar to that of the thymic swelling. Peyer's patches and solitary nodules were also hypertrophied. The spleen weighed 225 gm. and was about three times its normal size. The liver weighed 920 gm.

Cultures made from an inguinal gland remained sterile.

Microscopically, the kidney and liver revealed the usual small round cell infiltration of leukemia.

The question arises, What is this thymic swelling and what relation has it to the leukemia? Many cases of so-called mediastinal lymphosarcomas have been described. Such cases are usually characterized by infiltration into the surrounding structures and by giant cells, plasma cells, lymphocytes, etc. Hassall's bodies may or may not be present. The mass under consideration has a uniform lymphoid appearance; there are no signs of infiltration, and there is a thick fibrous capsule.

Sternberg[1] holds that in cases of leukemia characterized by a small type of lymphocyte, there is a general hyperplasia of the lymphatic apparatus, and that the cell in the blood belongs to the same type as those found in the lymphatic apparatus. That in those cases characterized by the large type of lymphocyte there is not this hyperplasia of the lymphatic system, but instead in many cases more distinct tumor-like formations, such as the so-called lymphosarcoma, chloroma, splenic tumor, etc., and that the cell in the blood stream is similar to the cells in the tumors. The so-called mixed cases he puts in the large cell group. In such cases about half the cells are of the small variety, the remaining of the large variety. Relatively the small lymphocyte has not increased to any marked extent and the large cell has increased many times; therefore

1. Sternberg: Verhandl. d. deutsch. path. Gesellsch., 1903.

it belongs to the large cell type. Many of these so-called mixed cases have definite tumors also.

According to this view the thymic swelling in the case of leukemia now under consideration, in which the cells were of the small type, may be regarded as a hyperplasia. Hyperplasia of the thymus in lymphatic leukemia is mentioned frequently in the literature, but instances in which the enlargement of the thymus approaches the extent of enlargement in this case appear to be rare.

Oct. 11, 1915.

DOUBLE MITRAL ORIFICE

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Herxheimer, in his article, "Missbindungen des Herzens und der grossen Gefässe," makes the statement that anomalies on the left atrioventricular ostium are very rare indeed and worthy of mention when found. The infrequency of atrioventricular malformation of the type reported in this article is indicated by the paucity of the recorded cases in the literature, a review of which reveals but nine instances of double mitral opening.

The first case is presented through the courtesy of Dr. H. G. Wells. The clinical data are very meager. The patient was a man 54 years old, of Norwegian nationality, a painter by occupation. He entered the Cook County Hospital Jan. 21, 1915, bleeding from the nose and mouth. Examination revealed some slight lung findings, but the heart boundaries and sounds were perfectly normal. The patient succumbed two days later from profuse hemorrhage. Necropsy was performed the following day. The anatomical diagnosis exclusive of the heart findings was:

1. Indurated ulcer of the lesser curvature of the stomach with recent hemorrhage from an artery in the floor of the ulcer.
2. Chronic interstitial nephritis (small red kidney).
3. Papillary adenoma of the kidney (confirmed by microscopical examination).
4. Sclerosis of the smaller arteries.

The heart (see Fig. 1) is of about normal size and weighs 350 gm. On its external aspect nothing abnormal is noted. The beginning of the aorta shows very few small sclerotic patches, but the aortic valves are normal and competent to the water test. The coronary arteries possess noticeably thickened walls but they are not atheromatous. No gross changes can be observed in the right half of the heart; the tricuspid valve appears normal, while the orifice is of the average diameter.

The myocardium of the left ventricle varies from 12 to 15 mm. in thickness. Examination of the mitral valve dis-

Fig. 1.—Congenital double mitral orifice. The accessory orifice is shown at A. Note the chordae tendinae attached to the margins of this accessory orifice.

closes a small, circular, fenestrated opening, 9 mm. in diameter, in the body of the posterior cusp. This segment is otherwise somewhat widened.

To the free margins of the flap are connected the chordae tendinae which are inserted in the posterior papillary muscle in conjunction with the chordae of the anterior segment. From the margin of the perforation indicated above are some delicate aberrant chordae which give the opening a fenestrated appearance, while the entire circumference gives origin to others which are inserted into the anterior papillary muscle and the ventricular wall. The anterior cusp pre-

sents no abnormal change. The foramen ovale is closed. No other lesion is observed.

Two openings are thus seen when the left heart is viewed from the auricular aspect, one large orifice, the atrioventricular ostium proper, normal in size and capable of being obliterated by the approximation of the valves, and a small fenestrated patulous perforation located in the body of the posterior cusp.

The finding resolves itself into a clear case of congenital deformity. A question arises as to the origin of the anomaly, so that a differentiation between a malformation and a deformity produced by endocarditis is pertinent. The possibilities to be considered regarding the latter etiology are an endocarditis occurring in utero or a postnatal endocarditis. Endocarditis in the fetus, however, occurs most frequently on the right side of the heart, and other manifestations of the disease besides those changes occurring in the heart are usually associated. In an aneurysmal rupture of the valvular segment from postnatal ulcerative endocarditis, the fenestrations seen in this case would be absent, nor would the chordae tendinae be arranged with such perfect regularity on the border of the orifice. The absence of other findings, such as sclerosis of the valves, pathological changes in the chordae, papillary muscles, endocardium and lining of the aorta, with none of the associated lesions in the kidneys and spleen which are often found in the ulcerative type of endocarditis, represents evidence against such etiology. An endocarditis producing a fusion of the valvular cusps at the point of contact, thus producing two orifices, might be considered were it not that the valve segments are free and except for the perforation perfectly normal.

A malformation occurring during the development in utero represents the most plausible interpretation of the anatomical findings. During development, the lower edge of the atrial canal becomes prolonged, normally on the left side into one, and on the right side into two flaps which project down into the ventricular cavities. An additional flap arises on each side from the lower edge of the partition of the atrial canal so

that three cusps appear on the right side and two on the left. Irregularly formed and accessory leaflets sometimes occur in the left heart. An explanation for the anomaly presented in the heart described can be offered by considering the posterior cusp here to be formed by the partial fusion of the tips and adjacent edges of two neighboring cusps. The fusion is incomplete where the second orifice appears. This suggestion is supported by the distinct widening of the posterior cusp and by the perfect arrangement of the chordae tendinae from the margin of the anomalous opening.

The statement from the clinical data that the heart boundaries and sounds were perfectly normal is interesting in view of the fact that the smaller opening was patent. The increased thickness of the left ventricular wall indicates a compensatory hypertrophy but can readily be explained by the chronic nephritis.

A review of the literature reveals eleven similar cases, a list of which is appended. Nine of these occurred in the mitral and two in the tricuspid valves. The extra orifices in the recorded cases are provided in all, except one instance, with their own cusps and chordae. In four of the cases the two orifices were of equal size and separated by a bridge of tissue. Two of the cases showed the second openings in the body of one of the valves. One specimen is reported as possessing a single large flap, the mitral valve, which covered a defect in the interventricular septum. Located 7 mm. back from the free margin of the large segment is a second opening which possessed two well-formed cusps. The remaining case or double mitral orifice reported by Abbott simulates somewhat the specimen reported in this article. There is an opening 2 cm. long in the aortic cusp of the main mitral orifice, leading into an aneurysmal pouch formed by the apex of this segment. The pouch communicates with the cavity of the ventricle by numerous fenestrations.

Camisà tenders the explanation that the condition of double mitral orifice is the result of a fetal endocarditis

which has led to a fusion of the apices of the valve segments so that two orifices are formed. The absence of sclerosis and associated lesions of the spleen and kidneys, together with the location in the left heart, render this explanation improbable. Cohn and Stuhlweissenburg suggest a simple malformation by excess and Pisenti interprets the condition as resulting from the "transmission of the blood during the early embryonic life, through fenestrations of the endocardial cushions," from which normally the valve segments develop. These fenestrations later become transformed into an orifice "by natural adaptation of growth, the cusps forming from its borders, and the chordae drawing together the edges of newly formed segments." This explanation fits in well with the case described above except that no cusps are present for the smaller orifice.

A question arises as to whether the secondary opening was functionally patent. The increased width of the posterior segment may have compensated the defect so that, in systole, the anomalous opening might have been along or above the line of contact of the mitral segments and thus rendered nonpatulous. That such may have been the situation is supported by the clinical examination which revealed no abnormal heart findings. The extreme weakness of the patient, especially important as the debility resulted from hemorrhage, however, renders the absence of clinical findings valueless in the decision of the functional patency of the anomalous orifice.

The second specimen (see Fig. 2) was found in a dog of which no record was obtainable, it having been killed in the physiological laboratory. The heart weighed 184 gm. Externally nothing abnormal was noted. The right half of the heart presented no pathological changes. There occurs, however, a perforation, about 6 mm. in diameter, in the body of the posterior mitral cusp, not located exactly in the center but somewhat anterior near the attachment of the valve flaps. From the circumference of this opening course

delicate chordae tendinae which unite and are inserted as one large cord into the ventricular wall. The free margin of the valve segment is provided with chordae possessing the normal attachments.

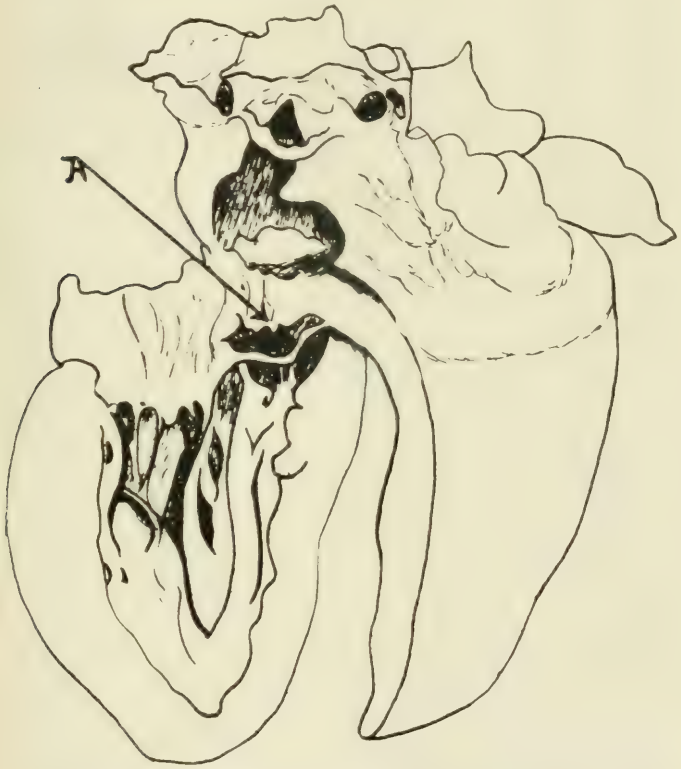

Fig. 2.—Congenital double mitral orifice (dog). Drawing is five sixth natural size. As the drawing is made with the heart in a vertical position the valve is seen only at the edge, the amount of valve tissue between the two orifices being much more than indicated here.

This second case resembles the first very closely. The openings have no cusps and consequently are patent. The perforation in the previous instance was located in the body of the posterior cusps, situated approximately in the center, while here the location,

although in the same segment, is eccentric, appearing closer to the valvular attachment and slightly anterior.

This specimen was complicated by a second phenomenon for which the heart was originally retained. In the left auricle, including the auricular appendage, there appeared many small whitish nodules, irregular in shape, in the endocardium. The distribution of the nodules was very extensive so that the entire endocardial surface of the auricle and its appendage showed a distinctly studded appearance. The nodules were of a delicate calcific consistency and showed slight variations in size. The deposits ceased rather abruptly at the mouths of the pulmonary veins, although there occurred a few circumscribed depositions in the intima; examination of the left ventricle reveals neither nodules nor sclerotic areas.

The most common sites of the deposits found in metastatic calcification are the alveolar walls of the lungs, the pulmonary veins, the left auricle and ventricle, the stomach and kidneys. The dominant factor concerned in the depositions of calcium in these situations, is, as pointed out by Dr. H. G. Wells, the concentration of the carbon dioxid of the blood and body fluids, the precipitations occurring in locations where the blood is poorest in carbon dioxid and, in the case of the stomach and kidneys, where acids are excreted; the alkalinity resulting from the removal of the acids favors the precipitation of the calcium. The widespread deposition of the calcium salts is thought to be due to an oversaturation of the blood with these salts which are derived from an excessive absorption from the normal calcium depots, such as occurs in tuberculosis and neoplasms of bone, and myelogenous leukemia. Usually, as in this case, the left auricle shows the most extensive calcification. Unfortunately the condition of the bones and other tissues of this dog is not known and hence the source of the calcification cannot be determined.

Oct. 11, 1915.

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CARCINOMAS OF THE NASOPHARYNX

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CHICAGO

The literature concerning the epithelial tumors of the postnasal space of which there have appeared reports of fifty-three was reviewed. The more exhaustive discussions of F. Laval (1905) and E. Oppikofer (1913) were referred to for the clinical course and differential diagnosis. Among the more important properties of these tumors mentioned were: (1) the insidious appearance; (2) the relatively slow growth considering the youthfulness of many of the patients; (3) the origin from (a) the covering mucosa of the nasopharnyx; (b) the mucous glands, and possibly from (c) the elements forming the pharynx-hypophysis or infundibular stalk; (4) the comparative youth of many of the patients, five of the fifty-three being under 17 years, several between 20 and 30 years, and the average age of the last twenty-six (collected by the author) a little under 40 years; (5) the usual absence of visceral metastases; (6) the fairly constant early cervical lymph adenopathy, and (7) the four routes of extension, that is (a) the inferior or pharyngeal, with cachexia from difficult alimentation; (b) the lateral, with middle ear disease from tubal obstruction; (c) the anterior or nasal, with involve-

ment of some or all of the accessory nasal sinuses and at times cranial extension; and (d) the posterior or cranial, with its symptoms of tumor of the base of the brain.

The failure of many surgeons and rhinologists to recognize the presence of these tumors was especially emphasized; also the great importance of properly examining the nasopharynx when there is no apparent cause for the cervical adenopathy elsewhere, and the frequency with which a diagnosis of tuberculous lymphadenitis and lues has been made when the glandular enlargement from the nasopharyngeal tumor was present.

He reported two cases of carcinoma of the nasopharynx with their clinical histories and course, clinical diagnoses, the changes found at autopsy and the results of a complete histological examination of the tumors and of all of the viscera. The first was in a physician twenty-six years old and the second in a boy nine years old. In both instances the glandular enlargement was the chief complaint and tuberculous lymphadenitis the primary diagnosis in the first.

At the postmortem examination of the first there was found extension into the orbits and about the sella turcica at the base of the brain, as well as extensive growth in the neck. The tumor in the boy grew chiefly by the inferior route and caused very marked edema of all the upper respiratory and alimentary passages, death being largely due to the stenosis of these passages. There were no visceral metastases in either instance.

Nov. 8, 1915.

REPORT OF A CASE OF CONGENITAL SYPHILIS OF THE HYPOPHYSIS

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Last year Dr. Menne presented before this society reports of cases of gumma of the hypophysis and collected about a dozen other cases from the literature.

A few months ago there was brought to this laboratory the body of a stillborn infant which showed marked lesions of congenital syphilis affecting the hypophysis and other glands of internal secretion. In looking up the literature of congenital syphilis of the pituitary body so few cases have been reported that a presentation of this case appeared to be worth while.

Ten cases of this condition have been reported in the literature (Simmonds, six cases; Schmidt, and Chiari, and Triboulet, Ribadeau-Dumas and Harvrier, and Dalpy, one case each). Schmorl mentions observations upon the hypophysis in congenital syphilis without giving details or stating the number of cases.

With the exception of the case of Schmidt, which showed a typical osteochondritis syphilitica and was unquestionably one of congenital lues, all the cases collected above have been reported since the discovery of the *Treponema pallidum*. Chiari was unable to find either tubercle bacilli or treponemas in the hypophysis in his case, but did not hesitate to call the lesion a gumma.

The case which I have to report is that of a full term stillborn infant brought to the laboratory by Dr. Athey, who furnished the following clinical history:

The father and mother were negroes and were aged 26 and 23 years, respectively. Both denied syphilitic infection and there was nothing detectable on casual observation to indicate that they had the disease. The mother, however, gave the history of having had, in the last three years, one miscarriage at five months, one miscarriage at about the eighth month, and the present case of a stillborn infant at term. At 1 p. m. the fetal heart sounds were heard. At the next examination at 6 p. m. no heart tones were audible. The child was delivered at 9:30 p. m. The position was left-occipitoposterior. The placenta (which was not brought to the laboratory) was friable and showed a few small infarcts. The amniotic fluid was turbid and of brownish color.

The findings at autopsy were as follows: The infant is a male and measures approximately 50 cm. in length. The body is well rounded out. Lanugo is almost entirely absent. There is no maceration. The head is large and a prominent caput succedaneum present. The fontanelles and sutures are

open. There is a spina bifida at the second and third lumbar vertebrae. There are no other external deformities or abnormalities.

The peritoneal, pleural and pericardial cavities contain no fluid and appear normal. The heart and large vessels show nothing noteworthy.

The lungs are uniformly pink in color and contain no air. There are no palpable nodules. The cut surface is of a uniform pink color throughout except that the walls of the bronchi and blood vessels appear somewhat thicker than usual.

The thymus extends from the sternal notch to the level of the fourth rib and measures 4.5 by 3 by 0.6 cm. The external and cut surfaces are of a uniform pink color. The mediastinal and mesenteric glands are enlarged, the former measuring 3 to 5 mm., the latter 3 to 8 mm. The superficial glands are not enlarged.

The spleen measures 6 by 3 by 1.5 cm. The cut surface is dark red in color and the normal markings indistinct. In places small lighter areas are just visible.

The liver is yellowish-red in color. On section the resistance does not appear to be increased. On cut surface the lobular markings are indistinct, but no nodules are found in any part of the organ.

The right kidney measures 4 by 2 by 1.5 cm. On cut surface the cortical markings are slightly obscured. The capsule strips with slight difficulty leaving a very finely granular surface, but not tearing away any of the parenchyma.

The left kidney is much smaller than the right and measures 2.5 by 2 by 1 cm. It shows several cysts from 1 to 5 mm. in diameter. The organ cuts with greatly increased resistance. The capsule strips with difficulty, bringing away parts of the kidney substance. The cut surface is pale and grayish and the normal markings absent. It is even difficult to make out a distinction between cortex and medulla.

The adrenals show a peculiar deformity in that the two are united across the middle line of the body. I have been unable to find records of similar malformations in the literature. A recent résumé of the subject of developmental anomalies of the adrenal by Miloslavich does not include any cases of this type. The left adrenal is larger than the right. The entire mass measures 3 by 2 by 0.8 cm. The capsule is probably slightly thickened, being more opaque than normal. Two small dark red areas, probably hemorrhages, less than 1 mm. in diameter are seen. The cut surface shows nothing noteworthy.

The external genitalia show no abnormality. The testicles are in the scrotum. The tunica vaginalis contains blood stained gelatinous material which adheres to the testicle.

The distal ends of the femur and humerus show typical osteochondritis syphilitica.

The convolutions of the brain are flattened. The lateral ventricles are greatly dilated and filled with clear fluid. The thickness of the brain substance in the parietal region is 2 cm.

The hypophysis measures 4 by 3 by 2 mm. No gross changes can be distinguished.

Microscopic Examination.—The most marked change in the hypophysis consists in a diffuse and very extensive increase of connective tissue. This change is limited to the anterior and middle lobes. The proliferation of the connective tissue is perivascular and lies between the dilated blood vessels and the cords of cells. As far as can be made out with Zenker-fixed tissues stained with hematoxylin and eosin the glandular elements consist chiefly of chromophobe cells with a fair number of basophilic and still fewer eosinophilic chromophile cells. The cleft between the anterior and middle lobes is dilated and contains masses of large cells with large pale and sometimes multiple nuclei and eosinophilic cytoplasm. Compared with the adult gland the posterior lobe appears to be smaller in proportion to the anterior lobe.

The testicle shows a similar diffuse intertubular increase of connective tissue much more marked than that in the hypophysis. There are also present an occasional plasma cell and a few areas of round-cell infiltration. In the connective tissue is seen here and there a large round or oval cell with a round eccentrically placed nucleus and abundant nongranular or, occasionally, vacuolated cytoplasm. Whether these represent the interstitial cells of Leydig is by no means certain.

The thyroid and parathyroid gland show the same diffuse proliferation of connective tissue. The thyroid contains no colloid. Some of the gland acini although dilated are empty.

The changes in the adrenal are very slight and consist in an occasional small area of hemorrhage and a few localized subcapsular areas of connective tissue proliferation. There are fewer and less extensive changes in the adrenals than in any other endocrinous gland.

The pancreas shows a most extensive proliferation of connective tissue with areas of round-cell infiltration and plasma cells. There are no gummas. The connective tissue change has in numerous instances involved also the islands of Langerhans. This is an infrequent finding. Stoerk observed a case of congenital syphilis in which the islands showed proliferation of connective tissue and occasional miliary gummas. This is the only case of the kind which I have found

described. A condition first described by Opie and later by Pearce and Stoerk is seen in this pancreas, namely, an apparent entrance of one of the gland tubules into the island of Langerhans. The explanation suggested by Opie and concurred in by Pearce and Stoerk is that in congenital syphilis, partly by the direct action of the virus and partly indirectly by the effect of the growth of connective tissue, the growth of the organ is retarded, so that the pancreas at term may resemble that of a fetus at the third or fourth month.

The thymus, unfortunately, was lost and no report of microscopic examination can be offered. There were no gross changes, however, in any way suggesting a Du Bois abscess.

The spleen is hyperemic. The perivascular connective tissue is increased in amount. There are several miliary gummas present, chiefly in the peripheral part of the organ.

The mesenteric and mediastinal lymph glands show perivascular connective tissue proliferation, the normal markings of cortex and medulla are obscured and there are present, especially in the medullary portion, large multinuclear cells.

The heart shows slight perivascular connective tissue proliferation, but otherwise nothing noteworthy.

The lungs show a marked increase in the perivascular and peribronchial connective tissue, but this change does not involve the parenchyma of the lung. The alveoli are collapsed for the most part, but a few are filled with a granular substance in which there is an occasional leukocyte or desquamated epithelial cell.

The left kidney, the smaller of the two, shows a most extensive increase of connective tissue involving practically all parts of the organ. A few hyaline glomeruli are seen. There are numerous cysts, the larger ones being lined by low, almost flat, epithelium, the smaller ones by low cuboidal epithelial cells.

The right kidney shows a very slight intertubular increase of connective tissue. Many of the vessels show mantels of round cells.

The liver shows periportal connective tissue increase with a very mild diffuse increase. There are areas of round cell infiltration, and many "proliferation cells" (Hoecker).

Treponemata pallida were found in great numbers in the adrenal, pancreas, including the islands of Langerhans, and left kidney. They were present in smaller numbers in the liver, thyroid, testicle, lungs, right kidney and heart.

Nov. 8, 1915.

EPIBRONCHIAL PULSIONS DIVERTICULA OF THE ESOPHAGUS

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In 1900 Brosch[1] described two diverticula of the esophagus, each into a space on the left side between

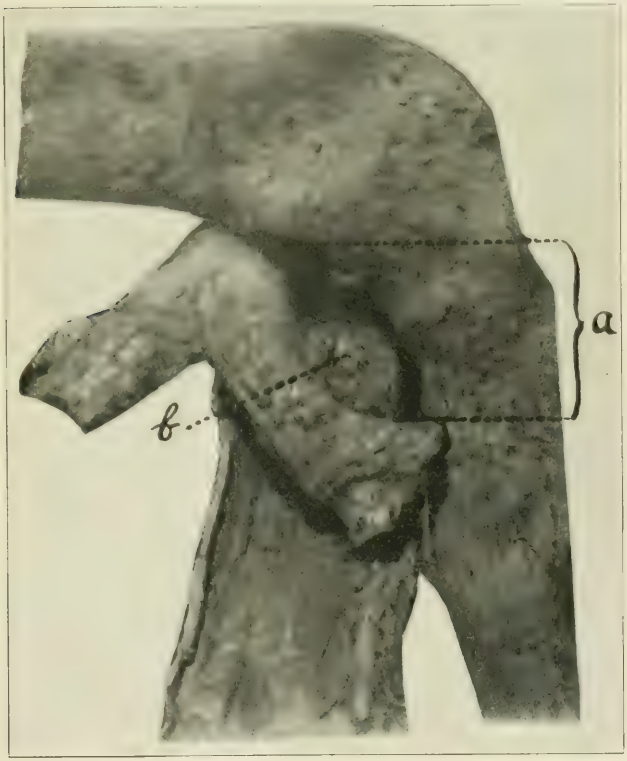

Fig. 1.—The diverticulum from in front in the broncho-aortic space. a. Cavum broncho-aorticum. b. Diverticulum.

the aorta and left bronchus, which he referred to as the *cavum broncho-aorticum*. As the aorta bending to the left and backward crosses the esophagus to its left

1. Virchow's Arch., 1900, clxii, 22, and 1904, clxxvi, 328.

side, there is formed this narrow place between the aorta and left bronchus where the esophagus is not in contact with firm structures like the aorta, bronchi or vertebrae, and it is assumed that food passing down the esophagus is under more or less compression by these

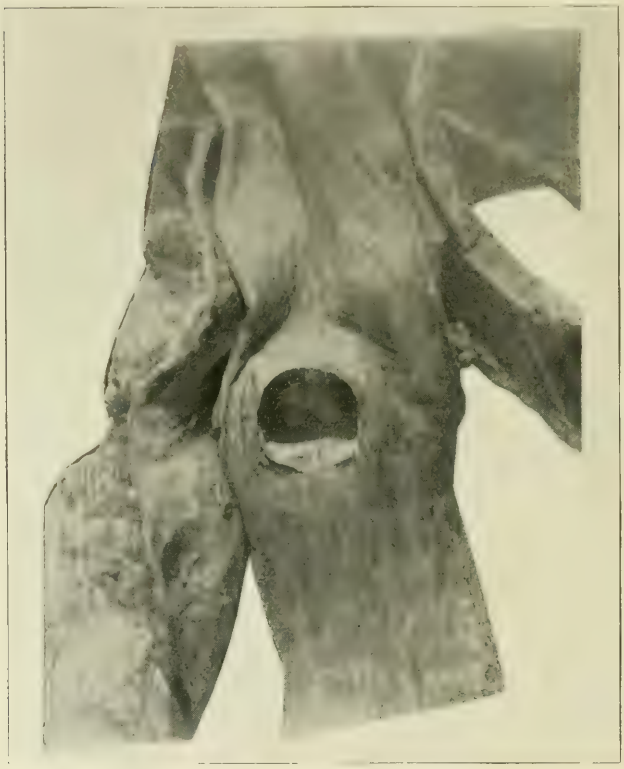

Fig. 2.—The pouch from behind.

firm structures, but arriving at this *cavum* there is greater opportunity for the esophagus to dilate and for pouching from internal pressure.

I have encountered three such sacs in the esophagus all unattached to lymph glands externally and all

unaccompanied by alterations in the adjacent tissues to suggest their origin by traction, all three into this vertical chink-shaped region. I have examined none of them microscopically to see what coats of the esophagus formed the pouch; one examined by Brosch was a hernia of the mucous coat through the other layers in the wall.

Two of these diverticula which I found were small. The example shown here (Figs. 1 and 2) was found in the body of an obese man, 55 years old, found dead with a dilated aortic root, practically an aneurysm, from changes regarded in part at least as syphilitic. The opening in the diverticulum is 1.5 cm. across and the pouch is almost spherical. Pouches such as these (and nearly all esophageal diverticula occur on the front wall) are best found by opening the esophagus behind.

Nov. 8, 1915.

SMALL BENIGN (?) TUMORS OF THE BOWEL

RAYMOND O. DART

During the past year the opportunity was given me to study five specimens of a very interesting group of tumors. They are the small, frequently multiple tumors found in the submucosa of the small bowel and appendix, which have been frequently discussed in the literature, especially German, under the classification, "carcinoma," "carcinoid," "accessory pancreas," "endothelioma," "epithelioma," and others.

The first case is that of a woman 27 years old who had suffered for a year with attacks of pain and tenderness over McBurney's point. She had no fever. A diagnosis of chronic appendicitis was made and the appendix removed.

There was a slight enlargement of the entire appendix. Its firm consistency led to the suspicion that a tumor might be present.

Microscopic examination leads one to believe that the tumor originated in the submucosa and grew out-

ward from this region into and through the muscular coats. On the mesenteric side the tumor cells have extended clear through into the mesenteriolum. A mass of scar tissue extends through the mucosa in places not occupied by the tumor cells. There are a few distorted remnants of the glandular epithelium on the side opposite the main tumor mass. The stroma is small in amount and is composed of fine strands of connective tissue with a few smooth muscle fibers. The cells in the central part of the tumor are arranged in rather large undifferentiated masses. Toward the periphery the alveoli are smaller and seem to lie in the lymph spaces. The endothelial lining of the lymph and blood vessels is greatly thickened. A few of the smaller peripheral alveoli are slightly differentiated into structures resembling gland acini. The cells are round or polyhedral and contain varying amounts of cytoplasm. Where they have shrunken away from the stroma the outer layer is frequently composed of cuboidal cells. A few are arranged in gland-like order. There are no ducts in these tumor masses. The nuclei are rather large, round and in places not too densely stained are seen to be vesicular in structure. They are for the most part regular in size and often eccentrically placed. No mitotic figures are seen. There is some round-cell reaction from the former appendicitis.

The following cases were kindly loaned by Dr. E. R. Le Count:

Case 2.—No history obtained, aged 59; death from starvation.

In the mucosa of the ileum, 165.5 cm. above the ileo-cecal valve is a round elevated area 2 mm. wide, 3 mm. long, and 1 mm. high. The mucosa is free over the mass. It has a resistant, elastic consistency. The surface made by section has a firm homogeneous consistency and is of grayish color; 125 cm. above this point is another umbilicated elevation 10 mm. long, 7 mm. wide, and 5 mm. high, with a circular depression, 5, 4, 0.5 mm. This mass is more resistant on cutting and the surfaces are soft and gray in the center with firm white edges. There are three other similar elevations still higher up, 9.2 cm., 43.7 cm., and 64.7 cm. These measure 2, 3, 2 mm., 2, 2, 1 mm., and 3, 2, 2 mm., respectively.

Sections of the largest show a well-defined tumor mass in the submucosa. No mucosa is seen over the surface of the mass. In places the tumor cells are between the muscle fibers of the bowel wall. There is considerable amount of dense stroma which in places where the alveoli are small resembles scirrhus carcinoma under the low power. The tumor cells are definitely epithelial in character and are seen in undifferentiated masses of varying size and shape. The nuclei are smaller, denser and slightly more irregular in shape than those described in the former case. Although the cells are seen infiltrating the muscle in places, there are no mitotic figures and there is no inflammatory reaction in the surrounding tissues.

In sections of another nodule the stroma is more abundant, the alveoli smaller, and the cells not so densely packed in them. There is considerable postmortem change and the cells are seen shrunken away from the stroma. A few small blood vessels are seen in the irregular cell masses. The individual cells are essentially the same as the cells in the other nodule except that the nuclei are slightly more irregular in size and shape. There are no karyokinetic figures and no evidences of inflammatory reaction. The tumor extends beyond the muscularis in radiating strands of alternate tumor cells and strands of connective tissue which converge into a contracted mass of scar tissue.

Case 3.—A white male, age unknown, died from pneumonia and interstitial nephritis.

Squarely opposite the mesenteric attachment 65 cm. above the ileocecal valve is a nipple-like projection into the bowel, 8 mm in diameter, circular in outline at the base and projecting 4 mm. into the bowel. On the serosa opposite this mass nothing can be seen except the faintly contoured outline of the tumor.

In sections the tumor is seen to be in the submucosa and to extend into the mucosa. In places the mucosa is gone, leaving the tumor cells exposed. There is considerable variation in the amount of stroma. Dense bands extend through the tumor in various directions, from which finer bundles form a network between the alveoli. This gives the tumor an uneven appearance resembling medullary carcinoma in places and scirrhus in others. The alveoli also vary in character. In the central portion they are similar to the others described. Toward the periphery there is some tendency toward differentiation. The cells are much more irregular in size and shape and there are differences in the individual nuclei. Careful search failed to reveal mitotic figures. The tumor does not extend into the muscle layers.

The next case is one of true accessory pancreas and presents certain interesting features in view of the fact that growths like these just described are regarded by many as accessory pancreatin tissue.

Case 4.—White male, age unknown, died from gunshot wound through the heart.

In the upper portion of the small bowel there is a yellowish region 2.5 cm. long, 1 cm. wide, opposite the attachment of the mesentery. The mesenteric glands are not enlarged. In the bowel directly opposite the region just described there is a ridge with its long axis parallel with the lumen. It measures 2.5 cm. long, 6 to 8 mm. wide and is elevated 5 mm.

In sections of this mass there is a thickening of the submucosa composed mostly of fibrous connective tissue and smooth muscle. The overlying mucosa is intact. Beneath the mucosa are several rests of pancreatic acini, differing but little from those in a normal pancreas. They are pin-head size and smaller, sharply defined, and imbedded in the stroma which makes up the thickening in the submucosa. There are no islands of Langerhans in these sections. Material for serial sections was not available. Near the periphery of each of these areas there are numerous small ducts. These are lined with regular columnar epithelium.

Nearby are small multiple fibro-adenomatous nodules, situated in the submucosa also extending through and displacing the muscle bundles. The longitudinal muscle layer is intact. These nodules are definitely circumscribed and are composed of fibrous connective tissue interspersed with a few smooth muscle fibers. The stroma is arranged concentrically around small areas of adenomatous tissue. These latter are composed of duct-like structures, varying in size, some dilated, others branching. The lumen contains a small amount of granular or homogeneous material. These ducts are lined by a single layer of high columnar epithelium similar to that in the pancreatic tissue. They correspond to the other adenomyomas of the intestinal tract except that the fibrous tissue predominates. No round-celled reaction is seen in the tumor. Such instances of accessory pancreas associated with adenomyoma of the small bowel have often been observed and for this reason many pathologists classify such adenomyomas as accessory pancreas even though no pancreatic acini can be seen.

Here, then, we have two, possibly three, distinct types of tumor. The accessory pancreas needs no

comment. There may be considerable difference of opinion concerning the others.

All observers do not agree as to whether the small appendix tumors are identical with those found in the small bowel. The appendix is the seat of tumor oftener than the small bowel. Also the tumors of the appendix are commonly associated with chronic inflammation, and present more of the characteristics of endothelioma. Then, too, they are found in younger individuals. The average age for appendix tumors of this type is 27½ years (Milner); for other parts of the bowel 45. This is questioned, however, by Oberndorfer[1] and others. Milner[2] concludes that they are the result of hyperplasia of the endothelial lining of the lymphatic vessels following chronic inflammation. Oberndorfer,[3] on the other hand, says that they are true epithelial tumors. He describes endothelial thickening in one of his cases and explains it is secondary to the tumor.

The character and genesis of the tumors of the bowel are still in doubt. Many regard them as excessory pancreas. Saltykow[4] has an interesting theory that they are pancreatic rests in which only the islands of Langerhans have persisted. Kaufman[5] thinks they should be called "epithelioma" unless they present evidences of malignancy and then they should be classed as carcinoma. According to Sternberg[6] they are of endotheliomatous nature, the lack of metastases and multiplicity speaking for a benign growth. Mallory[7] regards them as congenital malformations analogous to the nevi of the skin.

Recognizing the fact that these tumors are microscopically undoubtedly carcinoma, but unable to reconcile the carcinomatous structure with the clinical picture of a benign tumor, Oberndorfer[8] proposed the name "carcinoid" for them. Verse Oberndorfer[9] and

1. Oberndorfer: Verhandl. d. deutsch. path. Gesellsch., 1910, xiv.
2. Milner: Deutsch. Ztschi. f. Chir., 1909, p. 102.
3. Oberndorfer: Verhandl. d. deutsch. path. Gesellsch, 1910, xiv.
4. Saltykow: Beitr. z. path. Anat. u. z. Allg. Path., 1912, liv.
5. Kaufman: Spez. Path. Anat., Berlin, 1911.
6. Sternberg: Dis. Verhandl. d. deutsch. path. Gesellsch., 1910, xiv.
7. Mallory: Prin. of Path. Hist., W. B. Saunders Co., 1914.
8. Oberndorfer: Ztschi. f. Path., 1907, i.
9. Oberndorfer: Dis. Verhandl. d. deutsch. path. Gesellsch, 1910, xiv.

others, however, have reported instances of tumors of similar structure with metastases, hence of malignant nature. Kretz also saw a stenosing small bowel carcinoma which lacked round celled infiltration.

It would seem that the infiltrative rather than expansive manner of growth, and the occasional malignancy of such tumors warrant the conclusion that some at least are of carcinomatous nature.

Nov. 8, 1915.

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SOME REMARKS ON THE CEREBROSPINAL FLUID AND VITAL STAINS

LEWIS J. POLLOCK

The conveyance of substances to and removal of products from the central nervous system differs from similar functions in other organs in that the cerebrospinal fluid seems to be concerned in these performances.

It has been observed for a long time that substances find their way with great difficulty into the cerebrospinal fluid. Thus Mott[1] observes that arsenic, mercury and antimony do not pass the choroid plexus into the cerebrospinal fluid. Agglutinins of typhoid fever, bacterial toxins and hemolytic amboceptors do not enter the fluid. Following intravenous or subcutaneous or intramuscular injections of salvarsan, an infinitesimal quantity of arsenic, appreciable only by the most sensitive biologic test, has been found.

Goldmann[2] observed that following an intravenous injection of trypan blue solution the choroid plexus acts as a filter, many of its cells, pyrholzelle, being rich with stain and the brain and spinal fluid free from it. He considers that the large granular cells of the choroid act as protectors of the nervous tissue.

Frazier[3] reports a similar result in one of his experiments and Tilney[4] injected a cat intravenously with 1 per cent. solution of trypan blue and found after twenty-four hours that only the dura, pia and pituitary

1. Mott: Jour. Ment. Sc., lxi, 253, 175.
2. Goldmann: Arch. Klin. Chir., 1913, ci, No. 3.
3. Frazier: Jour. Am. Med. Assn., lxiv, April, 1915, p. 1119.
4. Tilney: Jour. Nerv. and Ment. Dis., 1914, xli, 454.

body was distinctly stained. None of the stain had penetrated into the cord. An intra-arterial injection showed marked staining of the liver, intestines, spleen, kidney and conjunctiva, but no stain of the central nervous system or its coverings. A subcutaneous injection showed the usual staining of the organs, but no region or part of the nervous system showed any stain.

The experiments noted above are based on the fundamental principle of vital stains first applied by R. Heidenhain, then developed by P. Ehrlich[5] in 1886, who discovered that with methylene blue certain parts of the nervous tissue stained selectively when subjected to this method. One source of error in the interpretation of such experiments should be mentioned. Methylene blue on contact with reducing agents in alkaline solution can be reduced to a colorless body, its leucobase. Now living or recently dead tissue elements are or may be both alkaline and very greedy of oxygen and thus act on the dye as reducing agents. The leucobase thus formed is easily reoxidized into methylene blue oxidizing substances, or acids, or even by the mere contact of air, which latter property is taken advantage of in histologic practice. The stain obtained by any of these methods (vital) is so unstable, that it begins to discharge after a short time, even in the living and not yet totally impregnated tissue.

Therefore it should be emphasized that although the nervous tissue may be stained intravitam by means of an intravenous or intra-arterial injection of certain stains, unless the stain be properly oxidized it may not be visible and if not properly fixed may fade out without having been observed.

Twenty various animals, dogs, rabbits and guinea-pigs were injected with various substances, trypan and isamin blue, methylene blue, malachite green and fluorescin.

From these experiments it was found that certain stains (methylene blue, malachite green) when intravenously administered enter into and may be demonstrated in the nervous tissue. That certain other stains

5. Ehrlich, Biologisch. Centralbl., 1886, vi, 214.

not necessarily of the composition of trypan blue (fluorescin) cannot be demonstrated in the cerebrospinal axis after intravenous administration unless they are introduced in a very large amount or after death. When the brain remains unstained under these conditions, certain other glandular tissues, as the testes, ovaries, suprarenal gland and pancreas, likewise remain uncolored.

Bouffard,[6] working with trypan blue and violet A of Nicolle and Meseul who, following Ehrlich, found that certain vital stains were trypanosomacides, reported likewise that certain glandular tissue, as testes, etc., remained unstained.

That the choroid plexus is not entirely responsible for the failure of stains to reach the cerebrospinal fluid is apparent when we recall that the cerebrospinal fluid is derived in part from the perivascular and pericellular spaces and it is not protected here by a barrier as would be supplied by a secretory organ as the choroid plexus. Another factor must be present. McIntosh and Fildes[7] suggest that the blood vessels of the brain possess an impermeability to certain substances peculiar to themselves.

Inasmuch as the blood vessels of the brain as well as those of the suprarenal body or the testicle show no histologic differences from those of other parts of the body, it would seem that the apparent impermeability of the blood vessels is due not to any structural or physiologic peculiarity, but to the fact that the tissues through which these vessels course, meninges and brain, have no chemical avidity for such substances as are circulating within them.

In conclusion, it may be said that it is not alone the filtering action of the choroid plexus which prevents certain substances from reaching the cerebrospinal fluid or nervous tissue, but other factors, such as the organotropic action of the drug or stain; and their absence from the cerebrospinal axis can be explained by no process differing from that explaining their absence from other glandular tissues.

Dec. 13, 1915.

6. Bouffard: Quoted by Levin, Jour. Med. Research, xxix, I, 1.
7. McIntosh and Fildes, Brain, xxxvii, 141.

PERITONITIS FOLLOWING ACUTE OVARITIS OF ANGINAL ORIGIN

RUSSELL M. WILDER

Hemogenic disease of the ovaries, arising by metastasis from disease of the tonsils or other distant foci of infection, is a condition which is probably far more common than is usually supposed, and may account for some of those cases of peritonitis which, because of their obscure origin, are referred to as idiopathic or primary peritonitis. Slavjanski,[1] Pfannenstiel[2] and others recognize the occurrence of ovaritis as a sequel of general sepsis, measles, typhoid, cholera and other infections, but the instances recorded are few and the general tendency of gynecologists is to consider ovarian disease as gonorrheal infection ascending from the lower genital tract.

The following considerations suggest that a considerable proportion of diseased ovaries are infected with streptococci rather than with gonococci, that these streptococcus infections are commonly blood-borne from some distant focus, and that certain cases of idiopathic peritonitis are in reality the result of such ovarian infections.

Rosenow,[3] by the use of special methods, isolated streptococci in fourteen out of twenty-five ovaries showing chronic and cystic degeneration. Riedel[4] has reported nine cases of purulent salpingitis in young girls who were operated on for suspected appendicitis. Fructus[5] and others have had a similar experience.

It is significant, furthermore, that of all the reported cases of so-called primary peritonitis, a strikingly large proportion have occurred in female patients. This is

1. Slavjanski: Bull. Soc. anat., 1886.

2. Pfannenstiel, in Veit's Handbuch der Gynäkologie, iv, 63.

3. Rosenow, E. C.: The Newer Bacteriology of Various Infections as Determined by Special Methods, THE JOURNAL A. M. A., Sept. 19, 1914, p. 903.

4. Riedel, quoted by Fructus (Footnote 5).

5. Fructus: Arch. gén. de chir., 1913, ix, 944.

true of primary pneumococcus peritonitis (Dieulafoy,[6] Lenormant and Licene,[7] Michaut[8] and Ehringer[9]), but to a greater extent of primary streptococcus peritonitis. Ehringer has collected ten instances, of which eight were in females. De la Chappelle[10] found twenty-one cases in the literature, and of these, sixteen were in females; De la Chappelle has reported in addition a series of twenty-three cases of peritonitis occurring during the course of an epidemic of acute sore throat at Helsingfors, and of these twenty-three cases, fourteen, or 61 per cent., were in females. A predilection for females so striking as this surely suggests that the sex organs play a significant rôle in these cases of primary peritonitis, and one wonders on reading over the recorded necropsies that more detailed attention has not been paid to the tubes and ovaries. Microscopic examinations are not mentioned, and the absence of gross changes is accepted as sufficient evidence of the normality of the ovaries. It is quite possible, therefore, that many such cases were primarily instances of ovaritis or salpingitis, and if this is true it is more than probable that they were metastatic infections from the throat, because in nearly every instance they occurred during the course of a tonsillitis.

In a very few of these cases the ovaries were carefully examined and the definite pathologic condition discovered. This is true of the reports by Leyden,[11] Kunzel[12] and Schwers.[13]

REPORTS OF CASES

Leyden's patient was a girl, aged 20, of previous good health, who fell ill, June 17, with vertigo, sore throat and fever. June 22, the general symptoms became markedly worse, and abdominal pains began. The patient died, June 28, with all the signs of acute peritonitis. Necropsy revealed a liter of purulent exudate in the abdomen, *edema of the ovaries, and*

6. Dieulafoy: Manuel de pathologoie interne, 1911, ii, 667.
7. Lenormant and Licene: Rev. de gynéc. et de chir. abd., 1905, lx, 225.
8. Michaut: Thèse, Paris, 1901.
9. Ehringer: Thèse, Paris, 1906.
10. De la Chappelle: Arb. a. d. Path. Inst. d. Univ. Helsingfors, 1907, ii, 583.
11. Leyden: Deutsch. med. Wchnschr., 1884, x, 258.
12. Kunzel: München. med. Wchnschr., 1904, li, 1920.
13. Schwers: Arch. de méd. d. enfants, 1914, xvii, 441.

reddening and swelling of the abdominal ends of the tubes. The sexual organs were virginal. The uterine mucosa showed a gray, pseudomembranous tumefaction; stomach, intestines and appendix were of normal appearance. *The tonsils were greatly swollen and congested.* No microscopic examination of the tissues was made, and the bacteriology of the infection was not studied, but the edema of the ovaries and swelling of the abdominal ends of the tubes suggests that they were the cause of the peritonitis.

Kunzel's patient, Maria B., was brought to the hospital in a state of unconsciousness. Subsequently a history was obtained to the effect that she had complained of a sore throat a few days before the beginning of her illness. Death occurred on the night of her admission to the hospital, and a necropsy was made. The bowel was hyperemic and especially congested in the pelvis. In the pelvis were 500 c.c. of a dark brown fluid mixed with flakes of pus. The appendix was only moderately hyperemic. The mucosa of the stomach, both large and small bowels and appendix was pale, and showed only slight enlargement of the follicles. Remains of menstrual changes were visible in the uterus. *The tubes were bright red, especially at their abdominal ends,* where they were distended with mucus and pus. On the contrary, their uterine ends were smaller and with small lumens. *The ovaries were deeply injected, and covered with a firm membrane. Both tonsils were enlarged to the size of walnuts.* Cultures from the peritoneal fluid yielded the *Streptococcus pyogenes* "var. long.," and from the tonsils the same organism. From the uterus a *Bacterium coli* and *Micrococcus pyogenes citreus* were obtained.

Schwer's patient, a child aged 2. with a grave peritonitis, when first seen had been ill for two days, constipated for twenty-four hours and vomiting for twelve hours. The temperature was 40.9 C. (105.6 F.), the pulse 168. The abdomen was tender and slightly resistant, both on the right and the left sides. An appendicular perforation was suspected, and the child was operated on at once. A thin nonodorous serous secretion was found in the abdomen. There were no adhesions, but some recent fibrinous exudate covered certain parts of the intestines. The intestines were everywhere hyperemic, the congestion increasing toward the pelvis, where it attained its maximum at the right tube. The appendix and other abdominal organs were intact. Death occurred four hours after the operation, and at the necropsy the following pathologic condition was observed: an *acute purulent infection of the entire genital tract, vulvovaginitis, endometritis and bilateral salpingitis. In addition, small purulent follicles were seen in the tonsils.* Bacteriologic examination of the

pus removed at the operation gave a pure streptococcus. The pus from the vagina contained only streptococci; there were no gonococci. The pus from the tonsils was not examined.

To these three cases I add a fourth, a personal observation.

Ruth B., aged 6 years, was seen, August 19, on account of a sore throat. For two days she had felt feverish. The bowels were constipated and the appetite was poor, but there was no abdominal pain. Examination revealed a temperature of 103 F., a flushed dry skin, dry lips, and a heavily coated tongue. The pharynx was hyperemic and the tonsils were large, edematous, hyperemic, and studded with discrete millimeter white patches. The lymph glands of the submaxillary region and those of the upper part of the posterior cervical triangles were enlarged and tender. In all other respects the examination was negative. August 20, the patient showed marked improvement, the soreness of the throat was gone, and the temperature was reduced to 99 F. She was not seen on the 21st, but from the mother's report felt perfectly well on this day until evening, when she had two loose bowel movements and complained slightly of pain in the lower part of the abdomen. August 22, she was found in a serious condition, with a temperature of 102 F., a rapid pulse, and rapid respiration. The abdomen was greatly distended, tympanitic and tender. This tenderness was greatest in the lower quadrants, but was *equal on the two sides.* There was no vaginal discharge. The right shoulder joint was tender but not swollen. The condition of the throat had improved. The urine contained no albumin or pus. A leukocyte count was 28,000, with polymorphonuclears comprising 90 per cent. A diagnosis of peritonitis was made, and although the prospects were unfavorable, the patient was operated on by Dr. Dwight Clark. At the operation the peritoneum was found hyperemic and lusterless, and in the pelvis was a small amount of thin pus. The appendix seemed normal. A drain was inserted, but the child died forty-eight hours later.

At the necropsy the following conditions were observed: The abdomen was distended and tympanitic, the intestines being ballooned with gas. A thin, serous, nonodorous exudate occurred in small amount in the pelvis. Both the parietal and the visceral layers of the peritoneum were very slightly hyperemic over the upper half of the abdomen, but were more intensely injected over the lower half and an angry red in the pelvis. A membranous gelatinous exudate 1 to 2 mm. thick occurred in the folds of the mesentery and covered part of the floor and walls of the pelvis. The intes-

tines showed no perforation, no volvulus and no diverticula. The cecum and appendix were slightly hyperemic, but with this exception appeared normal. The mucosa of the stomach and bowel appeared normal. The mesenteric lymph glands were uniformly enlarged and hyperemic. Liver, spleen and kidneys showed extreme cloudy swelling, but were otherwise normal. The gallbladder appeared normal. Microscopic examination of the ovary, tubes and uterus revealed in the tubes and uterus an extreme degree of hyperemia but no hemorrhages. In the lumen of the tubes there was no exudate. In that of the uterus was a small collection of leukocytes, half of which were mononuclears. *The ovaries showed, in addition to passive congestion, small hemorrhages, and in the ovarian tissues a few diplococci with short chain streptococci were found.* Cultures of the abdominal fluid obtained at operation resulted in the pure growth of gram-positive noncapsulated diplococci and short chain cocci belonging to the streptococcus group. The organism appeared on blood agar as a small, circular, moist colony, gray, and producing marked hemolysis. Its growth was best under anaerobic conditions. Inoculation into rabbits gave negative results.[14]

This case bears a striking resemblance to those of Leyden, Kunzel and Schwers. In all an ovaritis is suggested by the pathologic reports, and in my patient the anatomic diagnosis of ovaritis is certainly justified by the minute hemorrhages and the presence of diplococci in the ovarian tissues. In all four cases an associated angina suggests that the throat was the portal of entry of the infection. In all four cases a peritonitis developed. In all, the sequence of events seem to have been acute sore throat, later ovaritis and then peritonitis.

It is to be regretted that the other reported cases of so-called primary peritonitis did not have more attention directed to the state of the ovaries, as it would seem probable that acute hemogenic infection of the ovaries was the explanation of the peritonitis in many of them, and it is to be hoped that in all future cases of supposed idiopathic peritonitis the possibility of a hemogenic ovarian infection will receive consideration.

Dec. 13, 1915.

14. For this description of the organism and for the report of the animal inoculations I am indebted to Dr. F. W. Gaarde, and for the microscopic sections to Dr. B. O. Raulston.

BENIGN NEOPLASMS OF THE STOMACH

OSCAR NADEAU
AND
WILLIAM CARPENTER MacCARTY

Although the number of cases of benign tumors of the stomach is rare as compared to malignant tumors, they occur often enough to demand attention from the surgeon and surgical pathologist.

The early literature on this subject is not very reliable because of the fact that in many instances a microscopic diagnosis was not made. Among the benign tumors, the order of frequency has been reported as follows: myomata, fibromata, adenomata, lipomata, myxomata and cysts.

Morgagni[1] in 1761 first called attention to myomata of the stomach. They vary in size from a millimeter in diameter to tumors weighing 6,000 gm. They may be single or multiple and may be found in any portion of the stomach. They are usually derived from the smooth muscle coats and tend to grow either toward the peritoneum or toward the mucosa. They are spoken of as internal or external myomata. Occasionally gastric erosion ulcers are to be found in the mucosa covering them.

Farr and Glenn[2] reported a case which terminated fatally by hemorrhage. He reviewed the literature and collected eighty-four cases many of which did not, however, have microscopic diagnoses. F. Nassetti[3] found smooth muscle tumors in seven individuals who had died of some other disease. He makes a review of 140 cases. In ninety-five cases of one series 60 per cent. were found in males. There were two in boys and two in girls between 2 and 20 years of age; one man and one woman between 20 and 30 years; one man and eight women between 30 and 40; and

1. Morgagni: De Sed. et Caus. Morb. Epist., xix, Article 58, Venitiis, 1761, Tome i, F 191.
2. Farr and Glenn: New York Med. Jour., June, 1913.
3. Nassetti, F.: Tumori a fibre musculari liscie dello stomaco, Tumori, Rome, 1915, iv, 3, 260.

five men and thirteen women between 40 and 50. No correlation was evident between the tumors and clinical findings. Gastric ulcer was mentioned in four cases and in some there had been a long interval between the cure of the ulcer and the discovery of the myoma.

Our cases were classified as follows: leiomyoma 5, dermoid 1, adenoma 1, fibroma 3, adeno-leiomyoma 1, adenomatous hypertrophy mucosa 1, cyst 1, fibromyoma 2, making a total of 15 cases.

From Jan. 1, 1907 to July 1, 1915, the total number of cancers of the stomach operated on amounted to 1,194. During the same period there were fifteen (1 2/10 per cent.) benign gastric tumors other than gastric ulcers.

The clinical significance in our experience has been that of persistent partial or complete pyloric obstruction. In all cases, operative interference was made on the clinical diagnosis of pyloric obstruction with the great possibility of finding a malignant neoplasm. The acidity of the gastric contents was low except in those complicated by ulcer. As to age, the oldest was 75 years, youngest 8 years, the majority coming to operation between the fortieth and fiftieth year. Sixty-six per cent. were in males and 33 per cent. in females. The duration of symptoms was from five months to ten years.

Dec. 13, 1915.

EXPERIMENTAL HYPERCHOLESTEROLEMIA *

KAETHE DEWEY

The technical and experimental part of this investigation has been discussed in a previous publication.[1] Briefly stated, it is as follows: Twelve rabbits were

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* The complete article is being published in The Archives of Internal Medicine.

* From the Pathological Laboratory of Rush Medical College and the Otho S. A. Sprague Memorial Institute, Chicago.

1. Dewey, Kaethe: The Preparation of Colloidal Emulsions of Cholesterol, Trans. of Chic. Path. Soc., 1915, 321.

injected, intraperitoneally and intravenously, with watery colloid emulsions of cholesterol which was obtained from human gallstones. Three rabbits received intraperitoneally from one to seven doses of unfiltered emulsions, having concentrations as high as 5 per cent. In another group of three rabbits, intraperitoneal injections of finely filtered 2 per cent. emulsions were given either every day, or three times a week, for two, three and five months. Other rabbits were given intravenous injections of 1 per cent. emulsions regularly every day, or three times a week, for a limited period, while two rabbits were injected intravenously by an intermittent method with small amounts of cholesterol over long periods. The serum or whole blood, bile, and in several instances also the urine were analyzed for their cholesterol content by the method of Autenreith and Funk.

The presence of cholesterol which occurs in tissues in the form of liquid crystals, was studied in frozen sections from the liver, gallbladder, aorta, adrenal, spleen and kidney by the polarizing microscope and the sudan III stain.

In general, the histologic studies showed that very small quantities of cholesterol introduced directly into the circulation, are sufficient to produce infiltration and sometimes other pathologic conditions in various organs of rabbits. This cholesterol infiltration is not infrequently entirely out of proportion to the amount of cholesterol injected, leading to the conclusion that part of the cholesterol is spontaneously produced. This was especially noticeable in two rabbits which were injected by the intermittent method with such small total quantities as 2 gm. and 2.4 gm. cholesterol within 108 days. Pregnancy seems to furnish conditions which favor the infiltration with cholesterol, thus coinciding with the observation that in pregnancy hypercholesterolemia occurs physiologically. Cholesterol deposited in cells other than those normally and physiologically rich in this substance, are not a simple infiltration, but constitute an injury to the function of the cells and signify degenerative processes.

Unfiltered emulsions in which the colloid particles are of various sizes or consist of so-called "foam,"

and emulsions of high concentration, have a violent destructive effect on the parenchyma of the liver. This organ in rabbits is especially susceptible to infiltrative processes in experimental hypercholesterolemia. Practically all the rabbits showed a more or less extensive infiltration. Such a quick reaction does not in all probability correspond to anything occurring in man.

This observation has been considerably strengthened as the result of a more recent experiment. The cells, as has been repeatedly stated, which take up the granules of vital stains, are the same in which cholesterol is deposited. In rabbits saturated with trypan blue by intravenous or intraperitoneal injections, the blue granules are not only found in Kupffer and other endothelial cells, but also in the liver cells. In dogs treated in the same manner, the liver cells are not thus infiltrated.

The ready infiltration of the liver of rabbits with cholesterol is to be attributed to the fact that normally the elimination of cholesterol through the bile is very slight in herbivora. In carnivora the normal cholesterol content of the bile is high and cholesterol deposits have not been found in the liver of the cat, the dog and the white rat, even when fed with very large quantities of food rich in cholesterol. The liver is considered by some writers as the "regulating" organ in the cholesterol metabolism, inasmuch as it maintains the cholesterol equilibrium of the organism through the elimination of cholesterol by the bile.

Small concretions were found in the bile of the gallbladder in three rabbits. In another rabbit the gallbladder was filled with gallstones, twelve of them 2, 3 and 4 mm. in diameter; this rabbit had been injected intraperitoneally with 10 c.c. of a 2 per cent. emulsion every day for two months. A curious observation in this case was the almost total lack of cholestrol in the liver; evidently it was an exceptionally good filter, the cells being unusually permeable to cholesterol.

In no instance was there any indication of infectious processes in the mucosa of the gallbladder and it seems to be beyond question that gallstones were formed in sterile bile simply from an excess of cholesterol in the fluid. There is every evidence that the

presence of an abnormal amount of cholesterol in the bile of rabbits acts as an irritation on the epithelial cells of the mucosa; they desquamate and form the organic scaffold of the stones. Doubly refractive substances were not found in a single instance in the mucosa of the gallbladder nor in the lining of the bile ducts of the liver. Considerable quantities of a yellowish red stained material was found in widely distended lymph vessels in the gallbladder mucosa in several instances; it is probably resorbed from the bile. The chief analogy of value between these experimentally produced gallstones and those occurring in man lies in the association of gallstone formation with hypercholesterolemia. The latter occurs physiologically in pregnancy, due, as supposed, to retention through the liver. Immediately after delivery cholesterol is suddenly poured out in abundance into the bile. Aschoff[2] in particular calls attention to the observation that gallstones often occur in women during or shortly after labor. They are pure cholesterol stones, and as a rule of a noninflammatory origin.

The changes in the aorta were on the whole slight; cholesterol deposits in the intima, such as described by Russian writers, were not observed.

In the adrenals too great variations were found in the amount, distribution and state of division of the doubly refractive substances to permit of any conclusion. Sometimes the two adrenals in the same animal, in cholesterolized as well as normal and control rabbits, varied greatly as to the amount of cholesterol present.

Doubly refractive substances were scanty in the spleen of all the rabbits. Material, however, which stains yellowish red with sudan III was present more abundantly.

In the kidney, cholesterol infiltration and pathologic conditions were produced which hitherto have not been described nor attributed to experimental hypercholesterolemia exclusively. Weltmann and Biach[3] were able

2. Aschoff: Bemerkungen zur Arbeit von McNee, Deutsch. med. Wchnschr., 1913, xxxix, 995.

3. Weltman and Biach: Zur Frage der experimentellen Cholesteatose, Ztschr. f. exper. Path. u. Therap., 1913, xiv, 36.

to produce such an infiltration in rabbits fed with cholesterol only when they injected them also with uranium nitrate.

In the kidneys of the rabbits used for my experiments cholesterol was deposited in the form of extremely fine droplets, so very small that the dark central cross could not be observed under the micropolariscope. The tubules thus infiltrated did not flash up, but had a silvery hue; they gave the appearance of being powdered. They were yellowish red when stained with sudan III. The characteristic feature of the infiltration is that it is never diffuse, but always strictly focalized, generally restricted to the convoluted tubules. Often only a small number was involved, usually those in the immediate neighborhood of the glomeruli. These are, as a rule, not involved in cholesterol infiltration; only in the case where the infiltration and pathologic conditions were very marked, short silvery bands and curved lines flashed up under the polarizing microscope. Some degree of degenerative processes, although sometimes only slight, was associated with this infiltration in the majority of cases, such as vacuolization, disintegration and a desquamation of epithelial cells or atrophy of tubules. The changes in the glomerular tufts were as a rule slight.

A recent observation of the effect of trypan blue injections also confirms a repeatedly made statement that the identical cells which take up the vital stain also become infiltrated with cholesterol. The epithelial cells of the convoluted tubules in both dogs and rabbits are stained intensely blue from the large number of trypan blue granules which they have taken up. The glomerular tufts are practically free from the blue stain.

The conditions produced in some of the kidneys resemble somewhat those of the large white kidney in man. Microscopically, a typical picture was, however, observed only once. It will be of considerable interest to ascertain whether the nephritis occurring in pregnancy in which, as we know, hypercholesterolemia is a physiologic condition, is associated with an increased amount of cholesterol in the kidney.

Jan. 10, 1916.

A DEMONSTRATION OF AN ENLARGED THYMUS WITH AN ANOMALOUS LEFT VENA INNOMINATA

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The following observations were made on a case of thymic death which apparently falls in the group of status thymicus, and which is associated with a rare anomaly of the left vena innominata. Unfortunately, I did not see the case before death, and therefore have to depend on the statements of others, who did not make detailed observations, and on the rather incomplete clinical records on the history sheet. The history is as follows:

Full term pregnancy in primiparous woman 24 years old. Labor was long but normal in every other respect; presentation was cephalic, O. L. A. and terminated spontaneously in thirty-six hours. The baby breathed spontaneously and no difficulty in breathing occurred until about two hours after delivery, when it was noticed that the respirations were somewhat difficult and that the child was cyanotic. This condition prevailed for about two hours, when the cyanosis deepened, the respirations became more difficult and the child died. There were no convulsions and the heart tones were normal. Just before death the pulse went down to 30 per minute. No other observations of the baby's pulse were made. A tentative diagnosis of patent foramen ovale was made. A necropsy was performed five days after death, the body in the interval being kept on ice.

Necropsy recorded in brief:

The body is that of a well-nourished male infant 50 cm. long; weight 4 to 14 ounces. The skin of the head and neck, arms and thorax appears red and congested. There are no deformities. The superficial lymphatics are not enlarged. The testicles are descended. The head shows no signs of trauma.

On opening the body there is present a moderate amount of subcutaneous fat. Pericardial sac contains a large amount of serosanguineous fluid. Pleural cavities normal. Abdominal cavity negative. Left lung is compressed and pushed to one side by greatly enlarged thymus which is a heart-shaped organ situated slightly more to the left of the median line and extends from the lower border of the thyroid above to the fourth rib below. It is 4 cm. broad at its widest part and 5½ cm. long. Crossing the upper portion of the thymus from left

to right at the upper border of the clavicle to the level of the lower border of the first rib is the left innominate vein. This has compressed the thymus, and lies in a groove on its surface. A branch of this vein leaves the thymus tissues at about the midline of the body.

The inferior thyroid vein empties into the left innominata vein at the left border of the portion of the thymus lying above this vein. One fourth cm. above this junction the inferior thyroid vein receives a large branch from the thymus. There is no evidence of thrombosis in the thymic veins, left innominate, or superior vena cava.

The weight of the thymus could not be determined because of the desire to preserve the specimen intact. (Moreover, according to Scheele,[1] the weight of the gland has little to do with its power to compress the trachea.)

There are subepicardial petechial hemorrhages present in the heart, and it appears normal in size. The ventricular septum is intact, and the foramen ovale is closed by a septum.

The ductus arteriosus is present and patent.

The posterior portions of both lungs are markedly edematous in all lobes. The anterior portions are lighter in color and contain less fluid. Edema of the posterior portion of the lung is more marked on the left side.

The trachea was opened just above the upper edge of the main portion of the gland. There was evidence of compression of the trachea by the main body of the thymus, as shown by the difficulty of passing a probe downward from the opening compared with that of passing a probe upward from the opening.

The kidneys are normal in size, and show fetal lobulations. Cortical hemorrhages are noted.

The adrenals show no gross lesions and are not enlarged.

The liver and gallbladder are about normal in size and there are no gross lesions.

The spleen is normal in size, shape and consistency.

The stomach and intestines are negative.

Extremities are negative. There are no scars or deformities.

The cranial cavity was opened after the brain was allowed to harden in Kaiserling I solution for two days.

The head measurements were as follows: 13.5 M.O., 11.5 F.O., 9.5 S.O.B., 9.0 B.P., 8.5 B.T.

The fontanels are open.

The hypophysis is normal in size. There is no cerebral or meningeal hemorrhage and no evidence of inflammation or trauma.

Histologic examination made of the hypophysis, thymus, thyroid and adrenal and spleen revealed no abnormalities.

The anomalous vein in this case was the left innominate. This vein normally is situated posterior to the

1. Scheele: Zeit. f. klin. Med., B. 17, Suppl.

thymus and joins the right innominate to form the superior vena cava just above the bifurcation of the trachea. In this case the vein extended anterior to the gland and lay in a groove on its anterior surface.

This condition is not common judging from the number of reports in the literature. K. Hart[2] reports a similar case in which the thymus was normal in size. Von Mettenheimer[3] also reports a similar case and thinks there may have been compression between the gland and the sternum. Forrett[4] and D. Wornitschenke[5] each report a case and L. Rehn,[6] in commenting on von Mettenheimer's case, thinks that the vein came to lie anterior to the gland by causing pressure atrophy of the gland substance and cutting through from the posterior to the anterior side of the gland. Kayser[7] found a carotid extending over a prolongation of the thymus in the anterior surface of which it had cut a groove and the thymus tissue had been replaced by scar tissue.

The prolongation of the upper lobes of the thymus into the neck is considered anomalous by some authors and not by others. Thus L. S. Dudgeon[8] says: "The main portion of the gland is situated within the thorax, but both lobes send prolongations upward for a short distance into the neck sometimes reaching to the thyroid." Reiffel and LeMee,[9] in thirty-four cases found the thymus extending to the thyroid in one fifth of the cases.

Weber[10] and Kurtsteiner[11] found the prolongation of the right lobe most common, while Winslow[12] and

2. Hart, K.: Mitt. a. d. grenzgeb. d. Med. u. Chir., 1909, No. 12, p. 321.

3. Von Mettenheimer: Jahrb. f. Kinderheil., Leipzig, 1897, N. F., 26, p. 55.

4. Forrett: These de Paris, 1896.

5. Dwornitschenko: Vierteljahrsschr. f. ger. Med., F. 3, B. 14, 1897.

6. Rehn, L.: Arch. f. klin. Med., 1906, 80, p. 468.

7. Kayser: Inaug. dissert. Giessen, 1895.

8. Dudgeon, L. S.: Jour. of Path. and Bact., x, 174.

9. Reiffel and Le Meé, J.: Comp. Rend. Acad. des Sc., Paris, 1909, p. 148.

10. Weber: Hildebrand's Handbuch der Anat. des Mench., Braunschweig, Bd. 4.

11. Kursteiner: Anat. Hefte, 1899, B. 2.

12. Winslow: Exposition Anat. de la Structure du Corps Humain, Amster, 1732.

Cruchet[13] found the left lobe most frequently involved. The latter found this condition present in ten out of fifty nine cases, and says the thymus tissue is often represented by a fibrous band. Piersol[14] calls this band a suspensory ligament. In some cases (N. B. Harmon[15]), the gland tissue extends along the great vessels to the root of the tongue and bifurcation of the carotid. G. Bien[16] cites cases in which the gland tissue was intimately associated with the vagi nerves.

Aug. Hammar,[17] on the other hand, says that any elongation of either pole of the thymus is an anomaly and represents a reversion to the type seen normally in the lower animals, especially birds and reptiles.

Jan. 10, 1916.

CRANIOPHARYNGEAL DUCT TUMORS OF ERDHEIM

HARRY JACKSON

I am indebted to Dr. A. B. Kanavel for a specimen of a cyst of the hypophysial region which shows the following characteristics: the cyst lay in the sella turcica and was about the size of an English walnut. It contained about 3 drams of a chocolate brown fluid. A portion of the cyst wall showed on microscopic examination masses of stratified epithelium lying in a connective-tissue stroma. The epithelial masses have a border of high cylindrical cells which stain deeply (basal layer) underneath which are several layers of fusiform cells more lightly staining and between which, with the iron-hematoxylin stain, intercellular bridges can be seen (prickle cells). In short, the epithelium is of the type of buccal mucosa. The stroma is of an embryonic nature, being very rich in nuclei and blood vessels. Both stroma and epithelium show cystic degeneration, being very much like the

13. Cruchet: Bull. et Mem. Soc. Anat., Paris, 1901, Anneé 76, Sér. 6, T. 3.
14. Piersol: Human Anatomy, J. B. Lippincott & Co., Philadelphia, 1911, p. 1797.
15. Harmon, N. B.: Jour. of Anat. and Phys., Vol. 36.
16. Bien, G.: Anat. Anz., B. 29.
17. Hammar, Aug.: Ergeb. d. Ant. u. Entwickelungsgesch., 1909, No. 19, p. 1.

cell inclusions of buccal mucosa found in the jaw and forming the polycystic adamantinomas.

Keratohyalin, cornification, and cells of the hypophysis are all absent. The characteristics of this cystic growth correspond to those described by Erdheim[1] in 1904 as Hypophysenganggeschwülste or growths originating in "rests" or inclusions of the craniopharyngeal duct epithelium. A full discussion of these tumors, which are not commonly enough recognized, together with a table of all of the cases found in the literature, appeared in *The Journal of the American Medical Association* (April 8, 1916, lxvi, 1082).

Jan. 10, 1916.

DESCRIPTION OF AN UNUSUALLY LARGE PYOSALPINX

KENNETH HALLOCK

The specimen weighed at the time of operation 19¾ pounds; it was 17½ inches in length 22¾ inches in circumference at its greatest diameter. It was filled with a caseous yellow material, of the consistency of thick cream, which, on bacteriologic examination, was found to be negative for both aerobic and anaerobic organisms.

The external surface is smooth and shining, and well supplied with blood vessels, deeply injected, which radiate outward from the central point of the concave side. At this point the peritoneal covering is in two layers, between which lies the ovary, of approximately normal size, surrounded by a complete capsule, and containing a large blood clot and a corpus albicans.

It was not considered advisable to destroy the value of the specimen as such by making microscopic sections, but we believe that the specimen is a pyosalpinx, for:

1. It was attached to the cornu of the uterus, lying lateral and posterior to the uterus, corresponding in position to the left tube.

1. Sitzungsb. d. k. Akad. Wissensch. Math. Naturw., 1904, cl; cxxiii, 573.

2. The complete ovary is found, surrounded by its capsule, lying between the folds of the broad ligament.

3. Its shape is elongated and curved, differing in this respect from ovarian or tubo-ovarian cysts, which tend to have a spherical outline (Kelly).

In the literature we were able to find 302 cases of pyosalpinges in which, on bacteriologic examination, no living organisms were found (Menge, Morax, Schauta, Wertheim, Kelly).

A search through the available French, English and German literature of the last fifteen years failed to reveal any report of a tube approaching this one in size, although many large ovarian and tubo-ovarian cysts were reported.

Jan. 10, 1916.

A NEW ANTIGEN FOR COMPLEMENT FIXATION IN TUBERCULOSIS

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An ideal antigen for complement fixation for tuberculosis should be one derived from the tubercle bacillus itself, since this is the specific agent producing the disease. Reasoning similarly would bring us to concede that if the choice is given it would be preferable to use the material obtained from the tubercle bacillus that stimulates in the animal organism the production of the specific complement binding antibodies; in other words, the chemical constituents of tubercle bacilli liberated by their development and disintegration in vivo.

With this in mind the antigens used to date can be reviewed briefly and considered as to their specific value. One of the earliest antigens used was Koch's O. T. which was tried by Wassermann and Brück in 1906,[1] even before the discovery of the Wassermann reaction for lues. This antigen was found to be of practically no value for complement fixation. Koch's

1. Wassermann, A., and Brück, C.: Deut. med. Wchnschr., 1906, xxxii, p. 449.

B. E. was tried by a great number of observers (observations being begun about the same time as with O. T.) with better results. In an attempt to improve on the B. E. as an antigen a great many different antigens were prepared chemically, so to speak, and were highly recommended by those who have initiated their use.[2] Among these are: Calmette & Massol's[3] peptone soluble antigen, Besredka's antigen which Bronfenbrenner[4] lauds highly; Dudgeon, Meek & Weir's alcoholic antigen,[5] Craig's polyvalent egg media alcoholic antigen,[6] Hirschfelder's pepsin antigen,[7] not to mention the antigens prepared from tubercles and other tissues.

It is noteworthy, however, that the majority of the authors of which McIntosh, Fildes and Radcliffe[8] and Fraser[9] stand out conspicuously, admit that the best and least to be criticized antigen is an emulsion of living virulent tubercle bacilli. The former authors point out that the main fault in other antigens lies in the nonspecific reactions obtained which naturally give a higher percentage positive findings than the emulsion of living bacilli. This is shown especially by the fact that all alcohol prepared antigens and Besredka's antigen give positive reactions with luetic sera.

Since Besredka's antigen has been lauded so highly by certain investigators of late, McIntosh, Fildes and Radcliffe offer two other just criticisms of this antigen, and they are: first, the fact that no one but Besredka has thus far succeeded in making Besredka's antigen; and second, because an organism growing in so short a period of time as the organism used by Besredka must be questioned as to whether it is a true tubercle bacillus or not.

2. Stimson, A. M.: Bull. U. S. P. H. Service, No. 101, pp. 7-29, gives a good brief résumé of all the antigens used by various investigators up to 1915.
3. Calmette and Massol: Compt. rendue Soc. de Biol., 1912, lxxiii, 120-122.
4. Bronfenbrenner, J.: Arch. Int. Med., 1914, xiv, 786-803.
5. Dudgeon, L. S.: Meek, W. O., and Weir, H. B.: Jour. Hyg., 1914, xiv, 72-5.
6. Craig, Charles F.: Am. Jour. Med. Sc., 1915, cl, 781-90.
7. Hirschfelder, J. O.: Jour. Am. Med. Assn., 1915, lxv, 2057.
8. McIntosh, Fildes and Radcliffe: Lancet, 1914, p. 485.
9. Fraser, Elizabeth: Ztschr. f. Immun., Orig. 20, 1913, p. 291-299.

The value of autolysate antigens in complement-fixation tests already has been shown by a number of investigators, of which we may especially mention the work of Irons and Nicoll[10] in gonorrhea. The tubercle bacillus, however, differs from the gonococcus and rapidly growing organisms in a number of respects and it was, therefore, necessary first to prove that an autolysis occurs under suitable conditions, and second, that the autolysate could be used as an antigen for complement fixation tests. In a series of experiments, using the noncoagulable nitrogen, determined by the Folin micromethod as a criterion, it was found that tubercle bacilli suspended in sterile physiological salt solution and kept at incubator temperature gradually liberated nitrogenous products which were found in the salt solution. The curve of liberation of these products reached a maximum at about the eighth to tenth day as compared to heated controls. At room temperature no appreciable liberation of nitrogen was observed. The liberation of the nitrogenous products at incubator temperature occurred equally well under toluol, which kills the tubercle bacilli without destroying the autolytic enzymes. These experiments were carried out with both virulent human and bovine tubercle bacilli, so that it seems justifiable to call the product obtained by this method an autolysate.

In order to determine whether the autolysate from virulent tubercle bacilli was of any value for complement-fixation tests for tuberculosis and the relation between the nitrogen curve and the antigenic curve, a series of tests were carried out in which the noncoagulable nitrogen figure and the antigenic titer (that is, the minimum amount of autolysate solution necessary to cause complete fixation with a known $++++$ tuberculosis binding serum) were determined on the same autolysate solution at various periods during autolysis. It was found that coincident (although not absolutely so) with an increase in the amount of noncoagulable nitrogen found there was also an increase in the antigenic titer, so that an autolysate, to cite a specific case, which required 0.1 c.c. for complete

10. Irons and Nicoll: Jour. Infect. Dis., 1915, xvi, 303-310.

(++++) binding on the first day gave complete binding in 0.001 c.c. amount on the sixth day of incubator autolysis.

This antigen, prepared by autolyzing tubercle bacilli in sterile physiological salt solution and filtering through a Berkefeld candle, kept perfectly well without appreciable loss in strength for a period of six months or longer in the ice chest. When compared in a large series of both negative and positive sera with a bacillary emulsion (made from the same culture of bacilli) it was equal in value to the bacillary emulsion and did not possess the properties of interfering with clear reading of the reactions. The reaction obtained with autolysate antigen is also very stable, standing up perfectly well for longer than six to twelve hours after performing the test. The range of antigenic dose is also very large; for instance, an antigen giving complete fixation in 0.005 c.c. had no anticomplementary action even in 0.2 c.c. amounts.[11]

Jan. 10, 1916.

THE INORGANIC MATTER AND CARBON IN CHICAGO LUNGS

EDWIN F. HIRSCH

(From the Department of Pathology, University of Chicago)

Coal dust pigmentation of the lungs has been given considerable study, recently by Klotz,[1] whose review of the literature bearing on the subject contains most of the information available to date. It is not necessary, therefore, to take up such a review here, and this communication deals simply with a presentation of results obtained in the analysis of several lungs removed during necropsies performed by Dr. H. G. Wells on persons dying in the Cook County Hospital, Chicago. In addition to a quantitative estimation of the carbon, similar determinations were made of the calcium and silica content of these lungs.

1. Klotz: Pulmonary Anthracosis: A Community Disease, Am. Jour. Pub. Health, 1910, iv., 887-916.

11. A report of the findings obtained with the autolysate antigen will appear in the Journal of Infectious Diseases.

The methods used may be stated briefly as follows: The left lung was preserved as a museum specimen, while the right lung and the parabronchial lymph glands were ground up, weighed, and the dry weight determined after the tissues had been well desiccated. The dried tissues were then pulverized in a small coffee mill, and on this finely ground material all analyses were made in duplicate. The coal dust was estimated colorimetrically,[2] by comparing known quantities of toluol soot, finely divided, and suspended in liquid albolene, with the black residue obtained by digesting 1 gram of dried lung tissue with antiformin until the organic material largely had been removed, this then likewise finely divided and suspended in 10 c.c. of the colorless mineral oil. Following the digestion of the tissue with antiformin, the coal dust was thrown down by centrifuging in the usual way, washing with acid alcohol, then ether, and finally transferring the residue to a glass mortar with a little ether, this being evaporated over a steam bath. The carbon residue was then finely divided in the glass mortar, and suspended in the 10 c.c. of liquid albolene. The calcium and silica were determined gravimetrically according to a method outlined by Hans Aron.[3]

The results of these analyses are given in the appended table (Table 1).

McCrae,[4] after reviewing the data concerning the silica content of lungs, presents analyses of seven lungs, six of which were silicotic and had been removed from the cadavers of miners, the other having been taken from the body of a native Zulu, and was considered normal. The percentage of silica in the dried lung tissues varied between 0.73 in the normal to 4.47 in one of the silicotic lungs. The percentage figures obtained in the above tabulated analyses are below the one (0.73) considered as normal by McCrae. This, however, is of no great significance, for from the fact that the infant's lungs contain no silica, and that

2. Liefmann: Ueber den Nachweiss von Russ in der Luft, Habilitationsschrift Halle, 1907.

3. Abderhalden: "Handbuch der Biochemischen Arbeitsmethoden, Volume 1, 1910, 401-407.

4. McCrae, J.: The Ash of Silicotic Lungs, The South African Institute for Medical Research, 1913.

TABLE 1

Lung	1	2	3	4
Moist weight	365 gms.	284 gms.	427 gms.	438 gms.
Dry weight	80 gms.	70 gms.	96 gms.	78 gms.
Percentage of dry weight	21.92%	24.65%	22.48%	17.81%
Moisture percentage of moist weight	78.08%	75.35%	77.52%	82.19%
Ash	5.441 gms.	2.710 gms.	4.760 gms.	3.182 gms.
Ash percentage of dry weight	6.80%	3.86%	4.95%	4.08%
Carbon	2.72 gms.	0.71 gm.	1.20 gms.	0.19 gm.
Carbon percentage of dry weight	3.40%	1.01%	1.25%	0.24%
Silica	0.1748 gm.	0.2757 gm.	0.6895 gm.	0.0361 gm.
Silica percentage of dry weight	0.21%	0.39%	0.72%	0.04%
Calcium oxid	0.4483 gm.	0.1180 gm.	0.0170 gm.	0.0545 gm.
Calcium oxide percentage of dry weight	0.56%	0.17%	0.02%	0.07%

probably all of the silica which accumulates in the lung tissues comes from the exterior, as McCrae suggests, the amount of silica in a lung would be determined by the duration of exposure to and the silica content of an atmosphere. This same relation holds true in so far as the carbon content of the lungs is concerned, for carbon is recognized equally well as being of extraneous origin. This conclusion has developed from Boer's[5] quantitative determination of carbon in the lungs of individuals at various stages of life. He observed no darkening of the solution when the lungs of small children and fetuses were digested with antiformin. He states further, that the nature of the individual's occupation naturally exerts a great influence on the amount of coal dust inhaled and deposited in the lungs. Chimney sweepers and coal heavers must necessarily inhale more carbon particles than a sheep herder on some remote hillside. In the right and left lungs of a chimney sweep, Boer found, respectively, 8 and 5 grams of coal dust measured colorimetrically in terms of naphthalene soot. Klotz determined the carbon content of several lungs gravimetrically, 0.145 gm. for the right lung being his lowest estimation. This lung was removed from the body of a storekeeper (47 years old) necropsied at Ann Arbor, Mich. Compare this figure with 5.3 gm. determined in the left lung of a 28-year-old peddler necropsied in Pittsburgh. The minimum and maximum amounts in our analyses are, respectively, 0.19 and 2.72 gm., both estimations being for the right lung, and in all probability being typical for persons living in Chicago with occupations which do not expose them particularly to coal dust.

To illustrate objectively the amounts of carbon determined in the lung tissues, pieces of glass tubing, uniform in caliber, and sealed at one end were filled with weighed amounts of toluol soot corresponding to the determinations. The soot was pressed down firmly, and the tubes made comparative by making the column height directly proportional to the quantity of

5. Boer, W.: Ueber quantitative Bestimmung des anthrakotischen Lungenpigments, Arch. f. Hyg., 1911, lxxiv, 973-980.

soot. A small cotton plug was firmly packed into the tube and the open end sealed. In a similar way, equivalent quantities of calcium oxid were mounted, while for the silica, "Kiesel Guhr" was used. These tubes with the proper left lung were mounted on a glass frame and placed in a large museum jar in a manner similar to the usual method for displaying preserved specimens.

Jan. 10, 1916.

THE APPEARANCE OF SUGAR IN THE DIGESTIVE SECRETIONS OF PHLORHIZIN GLYCOSURIA

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It is generally held that phlorhizin produces a glycosuria by exerting a specific action on the renal mechanism. In the present research the salivary, gastric and pancreatic juices of normal and phlorhizinized animals have been examined with regard to their reducing power. In normal dogs, whose blood sugar was less than 0.13, no sugar could be demonstrated in the above juices. In the case of phlorhizinized dogs a reducing substance was found practically without exception in the pancreatic and gastric juice and often in the saliva. It was found that the presence of the kidneys is not necessary for the production of the phlorhizin effect, inasmuch as ligation of the renal vessels previous to the administration of phlorhizin does not alter the result. The percentile amount of reducing substance present in the juices was in all cases less than that present in the blood at the time of the collection of the juice.

The results in connection with the discovery of Levene, which has been confirmed by Woodyatt, that the bile of phlorhizinized animals contains dextrose, suggest that phlorhizin does not exert a specific action on the renal cells in the production of phlorhizin glycosuria.

Feb. 14, 1916.

LESIONS OF THE CENTRAL NERVOUS SYSTEM FOLLOWING INTRAVENOUS INJECTION OF BACTERIA

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Intravenous injections of bacteria from foci of infection about teeth and tonsils in a series of cases of intercostal neuralgia, postherpetic neuralgia and allied conditions, were followed commonly by striking lesions (hemorrhage, edema and leukocytic infiltration) of the posterior roots. The roots involved often corresponded roughly to those which appeared to be involved in the patient. In all of these streptococci were proved to be the cause of the lesions.

In a case of transverse myelitis with complete paralysis of the lower extremities, the bacteria from the pus pockets about the teeth and in the tonsils showed a pronounced affinity for the spinal cord, producing paralysis or great weakness chiefly of the hind extremities in rabbits, dogs and goats. The lesions in the spinal cord showed hemorrhage and perivascular infiltration in both gray and white matter, and leukocytic infiltration in the pia. These were most marked in the lumbar region. The lesions appear to be due to streptococci, even though mixtures of streptococci and colon bacilli were injected. The colon bacillus after isolation in pure form, failed entirely to produce lesions in the cord, while the streptococci still produced them, although its affinity was less marked than in the primary cultures.

The pus pockets in the tonsil in a case of typical sporadic anterior poliomyelitis in a young man with almost complete paralysis of both arms, was proved to contain bacteria which produced, on injection, paralysis chiefly of the front extremities in numerous animals. The spinal cord of these showed hemorrhages, especially in the anterior horns in the cervical region. The lesions in this case appeared to be due to a staphylococcus. Filtrates, injected intravenously and intracerebrally, of the broth culture, and of emul-

sions of the spinal cord and brain of animals showing marked hemorrhage, failed to produce lesions. The lesions in the animals were different than those found in epidemic anterior poliomyelitis in man and the experimental lesions in monkeys produced by Flexner and Noguchi, by intracerebral injection of the virus of epidemic anterior poliomyelitis.

It appears from these experiments that various diseases of the central nervous system, whose etiology is still obscure, are due frequently to bacteria which gain entrance into the blood from foci of infection, and which have elective affinity for the particular structures involved.

Feb. 14, 1916.

A STUDY OF THE BACTERIOLOGY OF CHRONIC PROSTATITIS AND SEMINAL VESICULITIS

HARRY B. CULVER

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In this study of the bacteriology of chronic prostatitis and seminal vesiculitis material was examined from patients suffering from one or both of the above conditions, together with a subacute or chronic arthritis. The anaerobic flora and a study of the specificity of the isolated organisms are of special interest.

Since the material examined must traverse an infective channel in securing it, the technic and controls are of very great importance. It has long been believed that the anterior urethra normally contains microorganisms and that the posterior urethra is sterile. Both aerobic and anaerobic organisms are present, as found by Pheiffer[1] and Jungana.[2]

Young, Geraghty and Stevens,[3] using a well controlled technic in examining nineteen cases of chronic

1. Pheiffer: Wien. Klin. Wchnschr., 1903, xvi, 762.
2. Jungana: La flore l'appareil urinaire, Paris, 1908.
3. Young, Geraghty and Stevens: Johns Hopkins Hosp. Reports, 1900, xiii, 271.

prostatitis isolated the *Staphylococcus albus* three times; streptococcus twice, and four unidentified organisms. However, only eight of their patients produced organisms on the single examination.

Notthaft[4] has found that repeated massage and bacteriologic examination is necessary before the infectious nature of some of these conditions is demonstrated, so, on the ground of a single examination a negative culture means but little.

Several others have done work on the aerobic flora of both prostatitis and vesiculitis, both with expressed material and that secured by operation, and the commoner pyogenic organisms are the ones most commonly isolated. Many times these investigators have seen organisms on direct smears, but have failed to get a culture on aerobic media.

Albarran and Cottet[5] isolated a very virulent anaerobic bacillus, the bacillus perfringens, from a prostatic abscess and report a second case of prostatic stone with infection, where an anaerobic organism was constantly demonstrated.

The anatomic structure of these parts, the constant presence of anaerobic organisms in the anterior urethra, as well as the possibility of invasion by contiguity or through the blood stream, make it seem reasonable to expect anaerobic as well as aerobic organisms present here in diseased conditions.

In this series there was clinical evidence of prostatitis or seminal vesiculitis in each patient examined and there was pus in the prostatic and vesicle contents at the time of examination. Patients with urethral discharges within six weeks were not used.

The technic used in securing the material was controlled by twelve patients with normal prostates and seminal vesicles; all giving sterile fluids.

Material was examined from thirty-four patients, twenty-six of these having arthritis, either subacute or chronic. Care was taken to use patients with no other foci that may be responsible for the arthritis, but this is not always possible.

4. Notthaft: Arch. f. Derm. u. Syph., 1904, lxx, 277.
5. Albarran and Cottet: La Presse Med., 1903, xi, 85.

Organisms were isolated from twenty-four (70 per cent.) of the patients examined. Twelve organisms were isolated as follows: *Staphylococcus albus,* nine times; anaerobic staphylococcus, once; anaerobic streptococcus, twice; gonococcus, four times; diphtheroid bacilli, three times; micrococcus tetragenus, once; colon-like bacillus, once; proteus bacillus, twice; micrococcus catarrhalis, once; unidentified Gram negative diplococcus, once.

In most instances these organisms were repeatedly isolated, as many as six separate bacteriologic examinations being made on a single patient.

As noted above, anaerobic cocci were isolated from four patients. After many transplants these became more aerobic, never growing as well as when under anaerobic conditions, however under all conditions, growing slowly.

Immunologic reactions were studied on twelve of the twenty-four patients. These tests, like all other phases of the investigation, were controlled.

In three of eight patients in which the skin test was tried, a definitely positive reaction was secured as compared with controls. In four of eight patients where macroscopic agglutinations were tried a positive reaction was secured with the patients' serum, in one instance as high as a dilution of 1 to 800.

The opsonin content of these patients' serum was normal or below, for the infecting organism, in six of seven cases examined. The seventh case had an index of two at the beginning. It is interesting to note that all, excepting this seventh patient, readily responded to injections of the killed organisms, with an increase in the opsonic index; the seventh one, however, showed no change in this respect, having the same index (2) after six injections.

When giving injections of killed autogenous organisms it was found that there was a very definite focal reaction in eight of the twelve patients examined, manifested by an exacerbation of the joint symptoms in seven of the eight patients, together with the onset or increase in genito-urinary symptoms, such as urethral discharge or changes in the act of urination.

The local and general reactions produced by these inoculations were very variable, but showed a distinct sensitiveness of the patient toward the infecting organism in about 90 per cent. of cases.

SUMMARY

Anaerobic as well as aerobic organisms may be the exciting cause of chronic prostatitis and seminal vesiculitis. This may account for the inability to isolate organisms by culture when seen on smears.

The organisms isolated in 66 per cent. of the patients tested, seem to be specific for the infected individual.

Many instances of prostatitis and seminal vesiculitis are apparently noninfectious on a single examination, but repeated examination often reveals the infecting organism.

These chronic infections seem to be partially or wholly responsible for many instances of subacute or chronic arthritis. The specific focal reactions obtained speak strongly in this direction.

Feb. 14, 1916.

SOME OBSERVATIONS ON THE ATYPICAL TYPES OF PNEUMONIA OCCURRING DURING THE SEASON OF 1915-1916

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During the recent epidemic of acute respiratory infections it was observed that the complicating pneumonias were quite atypical and did not correspond in clinical course or pathology with the ordinary type of lobar pneumonia. These atypical pneumonias usually occurred during or immediately following an attack of "grip," and were fatal, especially in the aged. The noteworthy subjective symptoms were profound exhaustion, severe thoracic pain, irregular temperature and dyspnea. The physical findings were usually very

indefinite, and often it was only a short time before death that any well-marked signs of pneumonia developed, and then only over a small area in the lung. The complications were quite numerous and the joints, serous surfaces, accessory nasal sinuses, gallbladder and appendix were the most common sites of infection.

The postmortem findings in these atypical pneumonias have been very interesting, and I am indebted to Dr. Wayne W. Bissell of the Cook County Hospital for much of my material for this phase of the study. The prominent gross pathologic changes were extensive hemopurulent pleuritis and pericarditis, marked hyperplasia of the lymph glands along the spinal column, including the posterior cervical, tracheobronchial, retroperitoneal, biliary and retro-esophageal group, marked mucopurulent tracheobronchitis, parenchymatous degeneration of the kidneys, liver and myocardium and petechial hemorrhages in the stomach, intestines, and pelves of the kidneys. The changes in the lungs were usually very striking, often the entire lung on one side being involved. This lung was usually only partially consolidated, very heavy and pliable. The interlobar fissures often contained encapsulated collections of thin bloody fluid. The cut surface of the affected lung was smooth and of a mottled grayish red and dark red color. The grayish areas varied in size and consistency, some being firm and dry, while others were very moist and often dripped a viscid blood material. These areas had no definite relation to the bronchi and were quite sharply outlined, resembling infarcts in appearance. Other dark red areas were very soft and a thick bloody material escaped from their cut surfaces. The general appearance of these areas suggested that they would have been abscesses if the case had not terminated fatally. In some instances there were numerous hemorrhages in the lung and the general appearance suggested gangrene. Other pulmonary findings were acute disseminated bronchopneumonia and all stages of lobar pneumonia.

In this work twenty cases of pneumonia were examined bacteriologically, all of which were quite different clinically from the ordinary type of lobar pneumonia and in most instances they represented sequelae of the current epidemic of "grip." In all cases the sputum was examined one or more times, in nine instances both the blood and sputum were examined, and in three instances cultures were made from the lung and heart's blood after death. The results of this work has been recorded in Table 1. In fifteen cases a virulent hemolytic streptococcus was isolated from the sputum and in three of these this organism was found in pure culture. Also this hemolytic streptococcus was isolated from the blood in three cases during life and from

TABLE 1.—THE ORGANISMS ISOLATED FROM THE SPUTUM OF CASES OF ATYPICAL PNEUMONIA

Organisms Isolated	No. of Cases in Pure Cultures	No. of Cases in Mixed Cultures	Total Number of Cases
Streptococcus Pyogenes	3	12	15
Pneumococcus	4	7	11
Streptococcus Viridans	0	7	7
Pneumobacillus	0	1	1
Bacillus Influenza	0	0	0
Staphylococcus Albus and Aureus	0	12	12
Micrococcus Catarrhalis	0	3	3

the lung and heart's blood in three cases examined after death. In eleven cases a virulent pneumococcus was isolated from the sputum and in one instance from the blood during life. But in only six instances were pneumococci and streptococci found in mixed culture. The blood cultures were negative in five of the nine cases examined. Other organisms commonly found in the sputum were green producing streptococci, fusiform bacilli, diphtheroid bacilli, and in one instance a spirillum was isolated from the sputum. Since a more detailed report of these findings will appear elsewhere it is sufficient to say that the gross pathologic findings as well as the bacteriologic observations indicate that the primary causative factor in these cases was a virulent streptococcus pyogenes.

The clinical and pathologic picture was that of a streptococcus bacteremia with metastases in the lungs as well as the joints, kidneys, serous surfaces, gallbladder and appendix.

Feb. 14, 1916.

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STUDIES IN THE ETIOLOGY OF CARCINOMA

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Cultures were made from the tissues of twenty-three human cancers, all being deep seated and free from ulceration. Portions of tissue from the central part of the tumor were selected for this purpose. From 15 of these (60 per cent.) a coral red or white torula was isolated. The organism grew well on agar media, best on agar containing glycerin or glucose. It is gram-positive. In smears of the tissues what appeared as the same organism was observed.

Subcutaneous injections (into guinea-pigs) of suspensions of the culture caused a local reaction with breaking down of tissue in ten to fifteen days, and healing in three to four weeks. Such guinea-pigs, killed after thirty days or dying spontaneously after five to nine months, exhibited grayish-white nodules in the lungs and liver from which the original organism could be isolated. The nodules microscopically partook of the structure of granulomata and epithelial neoplasms.

Ninety-six mice were inoculated with the torula cultures. In twenty-three tumors developed. The most common location was the lungs (seven times) and nodules in the liver were often associated. The mammary gland was involved next in frequency (five times), the lesions here being always on the side of the

inoculation, and microscopically appearing as adenocarcinomata. The organism was isolated from the nodules in the mice five times. It has been impossible to absolutely exclude spontaneous cancer in the inoculated mice.

Dec. 13, 1915.

MULTIPLE ABSCESSES CAUSED BY A STREPTOTHRIX

ALBERT HOWARD BAUGHER
(From the Pathological Laboratory of St. Luke's Hospital, Chicago)

Diseases produced by pathogenic fungi continue to create considerable interest. Many reports of isolated cases have been recorded and a number of exhaustive studies have been made of the more common forms. But notwithstanding this rather abundant literature, the study and identification of these organisms nearly always present difficulties. It is therefore the purpose of this paper to set forth the clinical picture of the patient in whom this organism was found and to give its cultural and morphologic characteristics.

Clinical History: On May 6, 1913, Mrs. Mc., aged 55, entered the private service of Dr. Arthur R. Elliott at St. Luke's Hospital suffering with a number of very painful subcutaneous abscesses which began to develop about one week before. She had experienced a feeling of exhaustion during the last five weeks. During this period she was frequently stuck by the thorns of rose trees and of cactus plants. She was also bitten by a species of large mosquito.

The examination of the patient revealed abscesses in the following locations: on the dorsal surface of the left foot just above the small toe, on the right external malleous, three small abscesses on the outer side of the right leg, one above the knee on the outer side of the right thigh, one on the left upper arm on the external side, and one on the right forearm on the outer side, and two small ulcerated areas above the left breast. All these lesions presented the same general characteristics and differed only in degree, some underwent resolution without becoming open ulcers, others had considerable pus. The abscess above the left small toe was the largest and most painful. This measured, before being molested,

1 cm. in height, 1.5 cm. in width and 2.5 cm. in length. It was extremely painful, fluctuated and was very red, though the zone of redness did not extend more than one-eighth of an inch from the margin of the elevation. This abscess was aspirated on May 7 with difficulty due to the thick mucoid pus present and on May 11 it was lanced. Smears and cultures were positive on each of these occasions. This lesion healed rapidly under hot boric dressings.

All the abscesses formed rather suddenly and about the same time, though a few new ones occurred at different times through a period of two or three weeks. The one on the dorsum of left foot was the first to occur and persisted the longest and was the only one that required lancing. The patient did not experience fever at any time and during a stay of one week in the hospital had only a slight temperature on two days.

The examination of the heart, chest, lungs and abdomen were negative. The chest was also negative to fluoroscopic and to Roentgen-ray examinations. No history of cough or diarrhea could be obtained. The blood pressure was 175. The urine was free from albumin, casts and sugar. Two blood cultures and one Wassermann test were negative. The red cells numbered 3,660,000, the leukocytes 8,000 and the hemoglobin was 75 per cent.

The treatment consisted of potassium iodid internally, and the application of wet boric dressings to the abscesses. The patient improved and left the hospital on May 17. Later reports showed that she completely recovered.

The Organism. — The organism was found in repeated smears and cultures on different days, as related in the case history, from the unopened abscess described on the dorsum of the left foot.

Direct smears from the original pus show the organism to be gram-positive, weakly nitric-acid-alcohol fast, well marked though not frequent branching, lightly and deeply staining areas in many of the filaments when stained with the ordinary stains, staining somewhat indistinct with methylene blue, filaments are inclined to be long and looping, though many are broken up into rods of various lengths. Slightly clubbed ends are found, also distinct swellings occur frequently along the strands. Many of the mycelial threads apparently are easily dissociated and when broken into short segments give the appearance of bacilli of various lengths. Not all the mycelial filaments stain unevenly as many take a uniform and deep stain throughout long lengths. It is apparently these segments that are most readily dissociated. Most of the short segments as do the clubbed ends and the

filament swellings take a deep and uniform staining. No sulphur granules were found. Smears from cultures stain in a similar manner to the above.

The cultures were made from material aspirated on May 7 and again on May 11 from material obtained when the abscess was lanced. Each time the abscess area was thoroughly cleansed with 70 per cent. carbolated alcohol and sterilized with several applications of tincture of iodin. Cultures on plain agar, blood agar, and 2 per cent. dextrose agar showed growths uniformly in about four or five days. When the colonies can first be seen they appear as little white dots on the surface of the media, and are firmly attached to it. They grow slowly, have a diamond-like brilliance due to a mucoid accumulation on each colony, gradually assume a brownish tint, and their circumference remains perfectly round with radiating strands which can be distinctly seen. These radiating strands appear to be branching under the ⅓ and ⅙ objectives, so that they form an apparent interlacing zone about each colony. The colonies have the general contour of a half sphere and at the end of ten days the largest colonies on blood agar (10 drops to 5 c.c. agar) measured only 0.25 cm. across. Those on plain agar being only about half as large. Transplants grow at about the same rate, even after three years cultivation. Surface growths on solid media do not coalesce except when the colonies are within the limits of growth of individual colonies.

Plain bouillon cultures grow more slowly than surface colonies on solid media and do not cloud the medium. Here the colonies assume a spherical shape about 2 mm. in diameter, with radiating strands extending in every direction. They may adhere slightly to the walls of the test tube, and after a time part of the colonies usually fall to the bottom of the tube while others may coalesce and form a mold-like scum on the surface of the media.

Laborious tubes on various media fail to develop colonies, except on or near the surface of the media and only after the media has separated from the tube by drying, do the colonies appear at deeper levels.

Cultures in litmus milk grew very slowly and slightly acidified the medium. Blood agar was only slightly hemolysed, if at all. A peculiar musky odor is uniformly given off from all the cultures.

Inoculation of large numbers of the organism fail to produce the disease in rabbits, guinea-pigs and rats.

The thermal death point in 8 per cent. sodium chlorid solution is under 55 C. for sixty minutes and under 60 C.

for fifteen minutes. The thermal death point under dry conditions is higher than 60 C. for sixty minutes.

It was possible to recover the organism from cultures which had stood at room temperature for a period of four months. These cultures were not protected in any way from drying, and apparently were free from moisture. Bouillon was added to each of eight dry agar cultures and growths were obtained in six at the end of three days. These organisms possessed the same characteristics as described above.

During an artificial existence of nearly three years this organism has acquired a greater degree of acid-fastness and is now almost acid fast as compared with the methods for destaining the tubercle bacillus. Ten per cent. nitric acid in 95 per cent. alcohol for three minutes slightly destain some of the apparently less dense mycelial threads; the denser filaments and the bacillary like form are still deeply stained. Neither does 25 per cent. sulphuric acid in water completely destain the denser forms, but after destaining for one minute with 30 per cent. nitric acid in 60 per cent. alcohol no organisms can be found.

The organism described above has been referred to by Dr. D. J. Davis in a paper read before the Eleventh Annual Meeting of the National Association for the Study and Prevention of Tuberculosis and is also very similar to an organism found by the same author in a pulmonary condition.

The thermal death point of the organism studied in my case falls well within the range as given by Foulerton and compares practically with seven of the species studied by him; nine of his species had a higher death point, ranging between 60 and 70 C. And according to Foulerton the thermal death point of my organism is practically identical with the strains of tubercle bacilli studied by Bangs.

Foulerton,[1] in one of his papers, gives statistics regarding the site of the primary focus of infection. Seventy-eight of these cases were from his own series, 109 from collected British cases by Osland and 632 collected cases by Ruhräh. These combined series comprise 819 cases, and in only sixteen, or in 1.9 per cent., was the skin the initial focus of infection. The primary site of infection occurred in the following locations in 761 cases, or in 92.9 per cent., respectively: (1) head, mouth and neck, 53.8 per cent.; (2) abdominal organs in 23.6 per cent.; (3) thoracic

1. Fouleston: Lancet, 1910, i, 551, 626, 771.

organs in 15.3 per cent. In the remaining 5.1 per cent. the site of primary infection was not specified.

These figures speak strongly in favor of the mouth or nose as the usual avenue of infection, though they do not exclude the possibility of primary skin infections. Foulerton mentions two specific cases in which bronchopneumonia with subcutaneous abscesses were described. One was reported by Sabrazès and Rivière and the other by Schule and Petneschky.

Foulerton,[2] Davis,[3] Wright,[4] Claypool[5] and others all state that this group of organisms does not have very definite characteristics. Foulerton goes so far as to say that apparently the organism under parasitic conditions is not acid fast, while under artificial growth it is acid fast. This seems to be partially true at least with the organism that I have studied, as artificial existence seems to have increased the acid-fast property.

The fact that all the lesions of this patient occurred on exposed and on external surfaces of the body speaks in favor of multiple cutaneous inoculations as the avenues of infection in this instance, rather than by embolic showers from some hidden lesion. Moreover, when the lungs or some of the other larger organs are the seat of the primary infection, metastases do not as a rule take place in the skin alone, but are found in the brain, kidneys and spleen as well.

The conclusion which I wish to draw in this paper is that the infection was due to multiple cutaneous inoculations, and that it remained local at these points.

Note.—I am indebted to Dr. Arthur R. Elliott for the privilege of reporting this case and to Dr. E. R. LeCount for the courtesy of the pathological laboratory at St. Luke's Hospital.

March 13, 1916.

2. Foulerton: Ibid.
3. Davis: Archives of Internal Medicine, 1914, xiv, pp. 1-7.
4. Wright: Jour. Med. Research, 1905, xiii, 349.
5. Claypool: Jour. Exper. Med., 1913, xvii, 99.

DEMONSTRATION OF A LEFT SUPERIOR VENA CAVA (PERSISTENT DUCTUS CUVIERI SINISTRA)

E. R. LeCOUNT

This accessory vena cava was present with the usual superior vena cava of the right side in the body of a man who died from phlegmonous inflammation of the neck and sepsis following an alveolar abscess.

There was no left innominate vein as generally is the case crossing the root of the neck to join the other veins of the right side, nor even a fibrous cord to represent it; nor was there any other communication in this region to anastomose the veins of the two sides draining the head and upper extremities. This left superior vena cava ran down in front of the left main bronchus and the blood vessels of the left lung to the sulcus coronarius on the left side of the heart, joining the sinus coronarius; in short, it was a typical persistent left duct of Cuvier. The obvious inference that persistence of this left ductus Cuvieri is brought about by failure of development of a v. anonyma sinistra to furnish anastomosis between the veins of the two sides is rendered in large measure untenable by observations[1] of double superior vena cava with a large communication of this sort, a left innominate vein, so that the blood from the left side of the head and from the left arm is free to course through either superior cava.

Indeed, as with many other anomalies, the variations are many, for in a few instances,[2] the left persistent duct of Cuvier after pursuing its usual course empties into a coronary sinus closed at its mouth and the blood from the coronary veins, left side of the head and left arm courses through the v. anonyma sinistra and right (usual) superior vena cava to the right auricle; the current in the left superior vena cava is then upward.

1. Case 2 of Schütz, Virchows Archiv, 1914, (216), 35.
2. Gruber: Virchows Archiv, 1885, (99), 492.

A persistent superior vena cava on the left side is one of the commonest of anomalies of the veins in this region. Marshall[3] in 1850 found thirty-one reported; in 1908, Ancel and Villemin[4] found eighty-nine, and of these in all but ten, like the anomaly shown here, there were two superior venae cavae; these ten were cases of a single superior vena cava, and on the left side, the usual one being absent.[5]

March 13, 1916.

BACTERIOLOGIC AND PATHOLOGIC EVIDENCES IN PAST GEOLOGIC AGES

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In the literature of vertebrate paleontology there are a number of incidental references to the diseased nature of the fossilized bones of fishes, reptiles, birds and mammals. The lesions represented in a fossil condition show a variety of diseases which are common today, indicating the great antiquity of disease. It is manifestly impossible to correctly diagnose, on the basis of our knowledge of modern diseases, the lesions which are preserved to us in a fossil condition. In the extinction of the ancient races of animals certain diseases without doubt became extinct with them, and it is partly the purpose of this study to inaugurate an inquiry into the nature of ancient diseases. No attempt has yet been made to study carefully all of the evidences of disease among ancient animals since these conditions, whenever noted, have been referred to only in an incidental way. It is no doubt true that the general processes of pathologic conditions will be found to be the same or at least similar in ancient geologic times and at the present time. Our studies to date indicate this clearly. We

3. Phil. Trans. Roy. Soc., (London), 1850.
4. Jour. de l'Anat. et Physiol. normal et pathologique, 1908, (44), 46.
5. Dietrich: Virchows Archiv, 1913, (212), 119.

wish also to point out that some of the diseased conditions to which man is today an heir may have originated back in the Paleozoic and the human race has inherited some of its troubles at least from the fishes and reptiles which lived many millions of years ago.

The diseases which have been cited among the fossil vertebrates are:

1. Caries, which is very common among fossil vertebrates and has been described by Renault[1] as occurring among Permian fishes 25,000,000 years ago. A large marine reptile, one of the Cretaceous mosasaurs, shows in the left mandibular ramus extensive evidences of the ravages of this disease. In an early Tertiary species of the three-toed horse the mandible has been affected by caries and possibly also by *actinomycosis,* as well as by *pyorrhea.* Caries has been noted in the jaw of a mastodon, and in the early cave bears of Europe.

2. Pyorrhea is especially evident in the absorbed alveolar margins and in the loosened teeth of a three-toed horse from the Miocene of North America and is also otherwise indicated in the cave bears.

3. Deforming arthritides are fairly common among fossil vertebrates and indicate a variety of pathologic conditions. The most prominent case of a deformed joint is the case of two caudal vertebrae of a large dinosaur, the interarticular surfaces of which have been extensively deformed and surrounded by huge exostosial growth. The enlargement is somewhat suggestive of the lesion of chronic osteomyelitis. It may be a callous growth possibly due to a fracture of the caudal vertebrae, or it may be a bone tumor. The mass resembles the tumor-like masses of oak trees. It entirely encircles the vertebrae and has involved fully half of the two bones. All evidences of separate structures are obliterated, and the two vertebrae are fused into a single mass. The specimen has a length of 26.5 cm. and a weight of 5.1 kg. The circumfer-

1. Renault, B., 1899-1900. Sur quelques Microorganismes des combustibles fossiles. Bulletin de la Société de l'Industrie minerale Saint-Étienne, Tomes 13-14, with folio atlas of 20 plates of untouched photomicrographs.

ence of the normal articular surface of one of the vertebrae measures 27 cm., and the same measurement around the middle of the tumor-like mass is 38.5 cm. The lesion has involved a length of 12 cm. Its surface is generally rather deeply pitted. There is an unusual ventral growth, which has carried with it the chevron, the bony process which served to protect the caudal vein and artery.

The condition sometimes spoken of as *rheumatoid arthritis* has been noted in the cave bears, in certain fossil human skeletons, in the famous Lansing man[2] of Kansas, and it is probably indicated in the Cretaceous mosasaurs.

A similar indication but of more extensive growth is evident in the cave bears of the Pleistocene of Europe which have been studied especially by Rudolf Virchow. Deforming arthritides are said to be quite common in fossorial mammals.

4. Osteomyelitis is indicated in the dinosaurian caudals described above, and in certain phalangeal elements from the Pleistocene of California.

5. Exostoses due to trauma, indicated as callous growths around fractures of ribs and limb bones, or as outgrowths due to chronic irritation or infection may be said to be fairly common. Broken and healed fractures are very common among mammals and are occasionally seen among fossil reptiles. Dinosaurs exhibiting broken ribs, vertebrae, horn cores, etc., attest the accidents or fights which caused these traumatic conditions and has led Abel[3] to infer that the males of these animals contested during the breeding season for the female. An exostosis which is especially clearly marked is evident on the inner or visceral surface of a dinosaur scapula where it takes the form of a hook-like process evidently due to chronic irritation. One of the most perfect indications of exostoses is seen in a mosasaur from the Cretaceous of

2. Parker, Charles A., 1904. Evidences of Rheumatoid Arthritis in the Lansing Man, Amer. Geol., Vol. xxxiii, pp. 39-42.

3. Abel, O., 1912. Grundzüge der Palaeobiologie der Wirbelthiere, p. 95.

Kansas where there is a decided lump at the articular surface between the third and fourth dorsal vertebrae.

6. Periostitis or some similar condition is evidently the cause of the production of exostosial growths in the humerus of a Cretaceous mosasaur from Kansas. It is also abundantly indicated in the limb bones of the *Soltaire,* an extinct quaternary bird allied to the dodo found on the island of Rodriguez, off the coast of Madagascar.

7. Osteosarcomata have not been positively identified among extinct animals but the condition is suggested in several instances.

8. Fistulae are evident in the lower jaw of an ancient and primitive whale from the Eocene of Egypt[3] and an enlargement of the mandible of a three-toed horse from the Miocene of North America indicates the presence of a fistula, possibly due to *actinomycosis,* in its early stages.

9. Rickets is indicated among the apes which are found mummified in the old Egyptian graves.

10. Necroses, due possibly to a variety of causes, and attributed by certain French writers to tuberculosis, are fairly common among fossil vertebrates. A marked necrosis of the ilium of a large dinosaur, accompanied by expansion and thickening of the bone, is evident in the mounted skeleton of *Camptosaurus*[4] on exhibition at the National Museum in Washington. A mosasaur bone from the Cretaceous of Kansas and certain crocodile limb bones from the Jurassic of England show lesions of necrotic nature. The assignment of any of the lesions to a definite cause is manifestly impossible, and while tuberculosis has been suggested as a possible cause the diagnosis is so uncertain as to be nearly worthless.

11. Hyperostosis or *pachyostosis,* which is similar to the enlargement of the bones in Cretanism, and is indicated as a thickened and enlarged part of the skeleton, has been detected in fishes and reptiles, some of them of great geologic antiquity.

4. Gilmore, Charles W., 1912. The Mounted Skeletons of Camptosaurus in the United States National Museum, Proc. U. S. Natl. Mus., Vol. 41, p. 689; pls. 56 and 58.

The study of Palaeopathology is just begun and what the results may be remains to be seen. It is, however, certainly of very great interest to find in past geologic ages, lesions which are so familiar to us today. If we can trace the lesions known to any definite cause among extinct animals, it will be a step toward the erection of the newest branches of pathology and dealing with the oldest aspects of that science.

Our knowledge of the bacteriology of past geologic ages is due largely to the researches of Renault[1] and his associates in France. The nature of many of the lesions seen in fossil bones likewise indicates or suggests the presence of bacteria. Renault described and figured many primitive forms of bacteria and fungi from the late Paleozoic and early Mesozoic rocks of many countries. He found these forms especially abundant in the fossilized feces (coprolites) of fishes, in ancient wood, and in coal. He also discovered in the teeth of certain extinct fishes indications of *caries*, as shown by the irregular decayed spots within the substance of the teeth. He shows in one of his plates some photomicrographs of fossil bone from the petrified feces in which the ravages of the bacteria are evident in the enlarged and distorted canaliculi and bone corpuscles.

Renault's work is the summing up of twenty-four years' activity during which time he investigated the nature of the micro-organisms in the following materials: (1) Peat, the age of which may be either a few years or many thousands of years. (2) Lignite or brown coal. (3) Recent bituminous schists in which he found rhizopods, bacteria and fungi. (4) Boghead coal. (5) Canal coal. (6) Ancient bituminous schists and (7) Silification of organisms in very ancient rocks. Evidences of bacterial activity are also found in the so-called ichthyodorulithes or fragments of bone which are found isolated in the rocks.

April 10, 1916.

ACUTE PRIMARY "IDIOPATHIC" PHLEGMONOUS GASTRITIS

EMANUEL B. FINK AND PAUL OLIVER

By this term is generally understood a purulent infiltration of the stomach wall, which most often localizes in the submucosa, and there leads to more or less extensive pus formation, but which may also affect the mucosa, submucosa, and serosa. The primary or idiopathic phlegmonous gastritis is the most frequently encountered, and our case also belongs to this class. It is not our purpose to review the literature on the subject as several excellent reviews are on record. Emge[1] in 1914 thought that only one half the cases reported, or about 50, were true primary or idiopathic phlegmonous gastritis.

The case herewith reported concerns a male, 58 years old, who was admitted to the Cook County Hospital in very poor physical condition. The man was obese and extremely weak. An operation was performed to reduce a double inguinal hernia. The patient did not make a good recovery, and developed symptoms of acute peritonitis. A laparotomy was then made, and after a careful search no perforation was found. At this time the stomach was found to be greatly thickened, and apparently the seat of the trouble. The wound was closed and drainage established. The man died on Jan. 19, 1916, shortly after the second operation, and within a few days after his admission to the hospital.

The postmortem examination was made on the afternoon of the same day by Dr. H. Gideon Wells, to whom we are indebted for the abstract from his necropsy records. The following is a description of the stomach as revealed by the necropsy findings:

The stomach shows a markedly hyperemic but smooth serosa, and on palpation shows diffuse thickening of the wall but no great induration. The thickening is not marked above the pylorus. On the lesser curvature is a point of irregular perforation limited to the serosa where a drainage tube was located. There are no adhesions about this perforation. On opening the stomach, the mucosa is seen to be diffusely hyper-

1. Transac. Chi. Path. Soc., 1914, ix, p. 82.

emic with hemorrhages beneath the mucosa. Folds of mucosa are missing. There is a purulent infiltration of all parts of the wall, and when cut creamy yellow pus oozes out. The infiltration extends from the cardiac orifice to the pyloric valve, where it stops abruptly. The mucous membrane is everywhere intact. The purulent material forms a layer apparently in the submucosa, 1 to 4 mm. in thickness, the pus oozing out slowly from the cut surface everywhere. The stomach is heavy and boggy, weighing 440 grams, emptied. No ulceration or tumor masses are visible. The mucous membrane is swollen and edematous. There is some hemorrhage in the mesogastrium, but no adhesions about the stomach. The diagnosis from histological preparations made from the wall of the stomach was acute interstitial phlegmonous gastritis, with marked suppuration of the submucosa and muscular coat, but no ulceration of the serosa. There was no evidence of injection in or about the herniotomy wounds.

A streptococcus hemolyticus was isolated in pure culture from the pus, both aerobically and anaerobically. All our attempts to produce this condition by animal inoculation failed, although the organisms were pathogenic. Rabbits, guinea-pigs, and dogs were injected intravenously; dogs were also injected directly into the stomach wall, but all without success.

This case and the bacteriological work will be published in full in the *Boston Medical and Surgical Journal,* Nov. 2, 1916. Recently another case of phlegmonous gastritis was observed by Dr. E. R. Le Count at the Cook County Hospital, and was studied by Mr. F. L. Glascock whose report follows.

April 10, 1916.

ACUTE PRIMARY "IDIOPATHIC" PHLEGMONOUS GASTRITIS

F. L. GLASCOCK

W. W., aged 50, unmarried American, plumber, was brought in an ambulance to the Cook County Hospital Jan. 27, 1916, to the service of Dr. Ryan. At the time of entrance into the hospital the patient complained of severe pain in the abdomen, most marked above the umbilicus. He became acutely ill two weeks previously with severe pain in the abdomen above the umbilicus in the midline. The pain was intermittent. About five days later the pain became excruciating. For five days he vomited everything he attempted to eat or drink. One day previous to entrance into the hos-

pital the vomitus was dark brown and very offensive. For three days the patient had no bowel movement and not more than one pint of urine was passed in that time.

The patient had no previous stomach trouble except occasional morning vomiting after drinking bouts. He had been constipated, the bowels moving about every four days. Venereal infection was denied. He drank periodically, smoked in moderation.

When seen on the morning of the 28th the patient was suffering intensely with abdominal pain. His face was bathed with perspiration and had an agonized expression. He was dyspneic. Deep breathing aggravated the pain. His limbs were cyanotic. The pupils were widely dilated. They were equal, reacting sluggishly to light. Pyorrhea alveolaris was very marked. No blue line was present on the gums. The tongue was heavily coated. There was no cervical adenopathy, no consolidation of the lungs. The heart boundaries were normal, the sounds were regular, no murmurs were present. The pulse was scarcely perceptible, it was running and of poor quality. The entire abdomen was tense. Central tympany was present and a diffuse tenderness most marked over the umbilicus. The urine was acid, containing some albumin, epithelial cells and a few hyaline and granular casts. The white cell count of the blood was 15,400. The patient was in profound shock. A clinical diagnosis of perforated gastric ulcer with general peritonitis was made. He was prepared for operation and was sent to the operating room and was operated on by Dr. Ryan. He died shortly after.

Anatomic Diagnosis (necropsy by Dr. LeCount).—Diffuse primary "idiopathic" phlegmonous gastritis, generalized serofibrinous peritonitis, paralytic ileus of small bowel, laparotomy drainage wounds of the abdomen, edema of the brain, marked distention of the subpial vessels, fatty changes in the liver, passive hyperemia of the liver, decrease in the yellow material of the adrenal cortices, moderate hypostatic hyperemia of the lungs, marked hyperemia of the larynx and trachea, moderate coal dust pigmentation of the lungs and tracheobronchial lymph glands, barrel-shaped chest, ossification of the costal cartilages. A statement made at the time of the necropsy is as follows:

"On the upper third of the stomach saddlewise and posteriorly there is a thickening of the peritoneum most marked in the upper part. There is a purulent exudate into the fat of the stomach wall which on sectioning allows a pale green fluid to escape."

The stomach wall was soft and doughy and greatly thickened, averaging 1 cm. The mucous lining was smooth, red

with submucous hemorrhages at the cardia and along the greater curvature. When cuts were made into the submucosa at any place a greenish-yellow pus exuded. The serosa and mucosa were of about normal thickness, the submucous layer was thickened five or six times normal.

Histologic examination showed no glandular change or change in the serosa. The normal appearance of the submucosa was lost, the structures having been replaced by fibrin, necrotic tissue and large numbers of polymorphonuclear leukocytes with a few large mononuclear leukocytes. The muscularis was very loose and edematous, the individual muscle bundles being widely separated. A gram-positive streptococcus was isolated by cultures from the pus of the submucous layer and was the only organism which grew or was found in either the cover-glass preparations of the fluid from the submucosa or in stained section of the stomach wall.

April 10, 1916.

A CASE OF GENERALIZED OIDIOMYCOSIS, ASSOCIATED WITH PULMONARY AND LARYNGEAL TUBERCULOSIS

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There are so few cases of systemic oidiomycosis with postmortem examination described in the literature that it is proper to record every case coming under observation. The one which we report herewith presents several unusual features which make it of particular interest. One of these is the co-existence of pulmonary and laryngeal tuberculosis with systemic oidiomycosis, involving, among other tissues, especially the lungs, larynx, prostate, and sacro-iliac synchondrosis. The last named lesion caused severe sciatic pain which dominated the clinical picture. So characteristic of tuberculosis is this distribution of the lesions that, in the presence of typical pulmonary and laryngeal tuberculosis, no suspicion was aroused at the autopsy that we were dealing with anything but an extensively generalized tuberculosis, in spite of the fact that one of us has had some experience with oidiomycosis. Even

the skin lesions were entirely compatible with tuberculosis. Only when routine histologic examination of the tissues was completed was the true nature of the case realized, and hence no cultures were made, and the central nervous system escaped examination. This emphasizes the possibility that other cases of oidiomycosis may escape detection, even when coming to autopsy, in the absence of routine histologic study of even what appear to be merely cases of tuberculosis.

The clinical history and necropsy findings of our case are as follows:

P. K., laborer, German, 32 years old, entered Cook County Hospital, on the service of Dr. Biesenthal, June 11, 1915. He complained of (1) constant dull aching pain in the right leg, of about two weeks duration; (2) hoarseness and a feeling of dryness in the throat; (3) productive cough, not present every day; (4) loss of strength and weight, and (5) night sweats.

Previous to November, 1914, the patient had been a farm laborer. At that time he came to Chicago, and was unable to secure work after that. Hygienic conditions were not ascertained. His present illness was first noted three months before entrance. Previous illnesses were pneumonia in 1905, and typhoid fever in 1911. The family history was negative; there was no history of tuberculosis. The patient used alcohol and tobacco moderately. Appetite was good and bowels were regular. Venereal infection denied. Urination was painful at times, and nocturnal urination was complained of.

Physical Examination.—The patient was emaciated, but was apparently in fairly good condition. The cheeks and eyes were sunken; the teeth were in poor condition; the supraclavicular spaces were sunken and did not fill with inspiration. Otherwise the head and neck were normal.

Chest: The chest was flat. The left lower portion was flatter than the right. The infraclavicular spaces were sunken. Expansion was poor over the apices and over the left lower portion. Tactile fremitus was increased over the right upper lobe. Resonance was slightly impaired over both apices. The left lower lobe was hyperresonant. Breath sounds were rough over both apices and over the right lower lobe posteriorly. There were a few râles over the apices. The voice sounds were bronchophonic over the apices. The heart boundaries were normal. The second pulmonic sound was accentuated. There was an ulcer 2 cm. in diameter on the right forearm of one year's duration, which was of suspected tuberculous

etiology. Examination was otherwise negative. Tubercle bacilli were not found in the sputum. The clinical diagnosis was pulmonary tuberculosis, sciatica on right side, tuberculous laryngitis.

The temperature was generally about normal, with a very slight afternoon rise. A few times a rise to about 101 F., of short duration, was noted. The pulse varied between 94 and 130, and was weak. Respiration was usually about 24, with fluctuation between 20 and 32. The patient rapidly grew weaker and death occurred July 5, 1915.

Necropsy was performed July 9, 1915, and the findings were as follows:

External Appearances: The body is that of an extremely emaciated man. The abdomen is sunken. The superficial lymph glands are palpable but normal in size. There is an ulcerated area over the middle of the right radius, 2 cm. in diameter, with sharply defined edges and a granulation tissue floor. There are some small superficial crusting areas over the right forefinger and about the right leg. There is no edema of the feet and ankles.

The abdominal cavity has no excessive fluid. The appendix is free from adhesions but the apical portion is thickened and moderately distended. The mesenteric lymph glands are conspicuous because of the total absence of fat, but they are not enlarged. The retroperitoneal lymph glands are normal. There are a few fibrous adhesions about the gallbladder. The diaphragm is at the fourth interspace on the right, at the fifth rib on the left.

Pleural Cavity: There are extensive adhesions between the lungs and the posterior surface of the sternum. The right cavity is obliterated by easily torn fibrous adhesions, except for the diaphragmatic surface. The left cavity is completely obliterated by dense adhesions. The mediastinal lymph glands are large, red, fibroplastic, but not caseous.

Pericardium is normal.

Mouth: The tongue is thickly coated. The tonsils are enlarged and contain a slight amount of purulent material.

Pharynx is somewhat reddened, without ulceration.

Larynx is swollen. There is very extensive ulceration and induration over the entire mucous surface; superficial ulceration over the folds of the epiglottis. The vocal cords are reddened, rounded, and their outline is obscured. The mucous membrane is ulcerated.

Trachea is filled with a blood-stained mucus.

Esophagus is normal.

Thyroid weighs 60 gm.; solid and rich in colloid. No gross lesions.

Heart weighs 300 gm.; the right auricle and ventricle are considerably distended; coronary arteries show a little beaded thickening with some patches of sclerosis; all the valves are normal; the aorta is free from sclerosis; the foramen ovale is closed; the myocardium is rather mottled, but there is no fibrosis.

Lungs: The right lung weighs 1,600 gm.; it is not collapsed, but is firm and solid. On palpation, the lower lobe is solid and does not crepitate; the consolidation is uniform; the middle and upper lobes are irregularly consolidated. On the cut surface all consolidated areas are studded with grayish granular nodules; there is much scar tissue in the upper part, surrounding calcified and caseous areas; there is no cavity formation; the apex consists of dense fibrous tissue.

The left lung weighs 1,500 gm.; consolidation is equal to that of the right; only the inferior third and a small part of the upper lobe crepitate. Cut surface: the apex consists of fibrous tissue with caseo-calcareous masses; elsewhere there are innumerable miliary nodules.

Liver weighs 1,500 gm.; it is of normal consistency and color; the cut surface has small, barely visible gray points.

Spleen weighs 260 gm.; there are small white areas all through the capsule; it is extremely flabby; the cut surface has many gray areas ½ mm. in diameter.

Gastro-Intestinal Tract: The colon and ileum show no ulcers. The appendix has thickened walls and the lumen is occluded in the proximal portion; the distal 2 cm. are distended with a clear jelly-like mucin.

Kidneys: Weight together, 420 gm.; both are alike; the cut surface is riddled with white nodules ½ mm. in diameter; the capsule strips easily; the external surface is also riddled with similar nodules; the pelves are free from ulceration.

Bladder has small tubercles and ulcers at the trigone; otherwise normal.

Prostate is approximately three times the normal size. A large necrotic mass with central softening, 5 cm. in each diameter, involves chiefly the right half; a smaller mass, 1.5 cm. in diameter, involves the left half; there is ulceration into the urethra from the prostate, 15 mm. long and 4 mm. wide, with superficial ulceration about this. The interior of the mass is entirely caseous.

Seminal vesicles are distended but not involved.

Testicles are normal.

Pelvis: In the retroperitoneal tissues is a fluctuating mass filled with purulent material extending from the promontory of the sacrum down through the right obturator foramen. The whole anterior surface of the sacrum is eroded and the

periosteum is necrotic. A pocket of soft eroded bone replaces the right sacro-iliac synchondrosis. The nerve trunks of the plexus are eroded. The process continues through the obturator foramen and about 6 to 8 cm. farther into the thigh, and extends upward to the upper margin of the iliac bone. The left sacro-iliac articulation is not involved.

Microscopic study of the tissues proved that the case, which clinically and at necropsy appeared to be tuberculosis, was one of generalized oidiomycosis together with pulmonary and laryngeal tuberculosis.

Skin ulcer has a granulation tissue base 0.5 to 1 mm. thick with considerable round cell infiltration; everywhere that granulation tissue is found, occur numerous round, slightly granular bodies with double contoured border, some of which appear to be budding; there are many polymorphonuclear leukocytes; the epithelial downgrowth with intra-epithelial pockets of pus, which usually occurs in chronic verrucous oidiomycotic lesions, is absent. No giant cells are found.

Lungs: Apex, diffuse fibrosis; great numbers of the oidiomycetes, many free in the alveoli, some in giant cells of the Langhans type. There are also encapsulated healed caseous areas, apparently tuberculous and containing no fungi.

Lower lobe: small areas of consolidation with giant cells are scattered throughout the section; the giant cells are smaller and the epithelioid cells are fewer than are usually found in miliary tubercles, and they do not present the zonular arrangement of tuberculosis. These areas of consolidation are swarming with oidiomyces, mostly free but some in fusion giant cells and some in large mononuclear phagocytes. Between the nodules the alveoli are filled with desquamated cells and detritus. There are also areas of fibrosis. In some areas of consolidation, fibrin is present. Some caseous areas do not contain oidiomyces and structurally resemble caseous tubercles, although tubercle bacilli cannot be demonstrated.

Peribronchial lymph gland has areas of acute infection up to 4 mm. in diameter, consisting chiefly of polymorphonuclear leukocytes and oidiomyces, with a little fibrin. Marked hyperplasia of endothelioid phagocytes, and many red corpuscles in the sinuses.

Larynx has many small typical tubercles with Langhans giant cells, in the subepithelial connective tissue; tubercle bacilli present in these giant cells; erosion of the epithelium and granulation tissue formation; no oidiomyces found. These lesions are typical of tuberculous laryngitis and do not at all resemble the lesions of oidiomycosis elsewhere in this body.

Thyroid contains several microscopic areas of typical oidio-

mycotic infection. These contain many organisms and present the same histological features as the lesions described elsewhere.

Prostate is nowhere normal. Nearly all the acini are distended with masses of leukocytes, desquamated epithelium, and oidiomyces. In many places the tissue is necrotic and large abscesses are formed. Extensive interstitial leukocytic and round celled infiltration.

Seminal vesicles do not show any evidence of infection.

Kidney has many small necrotic foci with oidiomyces present; in these foci there is polynuclear and round celled infiltration, and a few epithelioid cells. These areas are found in both cortex and medulla. In the pyramids are tubules greatly distended with masses composed almost entirely of oidiomyces. Some of the abscesses definitely began as glomerular lesions.

Liver has many lesions, mostly microscopic, where the liver cells are necrotic and replaced by inflammatory cells. Some of these lesions contain oidiomyces. Others do not, and the latter in structure closely resemble miliary tubercles.

Spleen has many necrotic foci containing the oidiomyces, with leukocytic and endothelioid cell reaction; no typical tubercles present.

Section from sacrum shows extensive necrosis of both bone and marrow tissue with leukocytic reaction. Both the dead tissue and the reactive zone are swarming with oidiomyces, mostly free, but occasionally in small giant cells.

Pelvic cellular tissues are mostly necrotic, with areas of leukocytic infiltration and hemorrhage; everywhere oidiomyces are swarming.

Anatomical Diagnosis.—Generalized miliary oidiomycosis involving especially the lungs, spleen, and kidneys; suppurative oidiomycosis of right sacro-iliac synchondrosis, with extensive suppuration of regional muscles and fascia extending through the right obturator foramen; extensive oidiomycotic abscess of prostate, with perforation into the urethra; superficial ulceration of the urinary bladder and prostatic portion of the urethra; hyperplasia and oidiomycosis of intrathoracic lymph glands; oidiomycotic ulcer of the skin of the right forearm; multiple crusting, superficial ulcerations of the skin; colloid goiter with miliary oidiomycotic lesion of the thyroid; old fibrocaseous lesions of both pulmonary apices; ulcerative and miliary tuberculous laryngitis; bilateral obliterative fibrous pleuritis; dilatation of the heart; retention mucous cyst of the vermiform appendix; general emaciation.

This case, then, is evidently one of generalized oidiomycosis associated with pulmonary and laryngeal tuberculosis. Only two other cases of combined infection have been found in the literature, a case reported by Ormsby,[3] and another in the *New Orleans Medical and Surgical Journal* Symposium.[7] Other features of interest in this case are: the extensive involvement of the prostate with only slight urinary symptoms, the involvement of the thyroid, the extensive pelvic abscess and sacro-iliac infection with severe sciatic pain, the lack of other bone involvement, the lack of subcutaneous abscesses, and the close clinical and gross anatomic resemblance to tuberculosis. Apparently this is the first case in which thyroid lesions have been observed in oidiomycosis, which is probably to be explained by lack of examination of this tissue in other systemic cases, rather than by a special insusceptibility.

Complete reviews of the disease, with pathologic, cultural and clinical characteristics, and case reports, have been made by Ricketts,[1] Hektoen,[2] Montgomery and Ormsby,[3] Harter,[4] and Stober.[5] Brown and Cummins[6] have reported an exhaustive study of the organism, together with a comparison of blastomyces with coccidiodes, and mention a case not yet reported. A symposium on oidiomycosis reported in the *New Orleans Medical and Surgical Journal*[7] gives synopses of clinical histories of five systemic cases occurring in New Orleans, with autopsy of four. Dr. Hurley also reports separately[8] the occurrence of myocardial lesions in one of these cases.

Altogether, we have been able to collect from the literature thirty-five cases of generalized oidiomycosis, besides our own. While this article was in press there

1. Ricketts: Jour. Med. Res., 1901, 6, 374.
2. Hektoen: Systemic Blastomycosis and Coccidioidal Granuloma, Jour. Am. Med. Assn., 1907, xlix, 1071.
3. Montgomery, F. H., and Ormsby, O. S.: Systemic Blastomycosis, Arch. Int. Med., 1908, ii, 1.
4. Harter: De la blastomycose humaine, Nancy, 1909.
5. Stober: Systemic Blastomycosis, Arch. Int. Med., 1914, xiii, 509.
6. Brown and Cummins: Coccidioidal Granuloma and Blastomycosis, Trans. Assn. Am. Phys., 1914, 29, 628.
7. Symposium on Blastomycosis, New Orleans Med. and Surg. Jour., 68, 1915, 287-311.
8. Hurley: An Unique Lesion of the Heart in Systemic Blastomycosis, Jour. Med. Res., 1916, xxxiii, 3, 499.

appeared a paper by Wade and Bel[9] summarizing forty-two cases they were able to collect. Their report does not include Harter's case. Six of these additional cases were more or less completely autopsied, and we must add to the above figures the following correction: lungs, 5; spleen, 3; kidney, 3; lymph glands, 1; liver, 1; brain and meninges, 2; pleura, 2; prostate, 1; pancreas, 1; adrenal, 1; pericardium, 1; larynx, 1; epididymis, 1; tongue, 1; tonsil, 1; esophagus, 1; diaphragm, 1; testicle, 1. The five cases reported by Wade and Bel are these reported in the "Symposium on Blastomycosis" referred to above.[6] In twenty-three of these thirty-six cases, autopsy has been performed. Besides these, over a hundred cases of skin involvement have been reported. There are also in the literature several cases of isolated involvement, as in the female genitalia (Van der Velde), the buccal cavity, etc., but in some of these the organisms were only incompletely identified, and the disease was not systemic; therefore they are not considered here. In the cases autopsied, including our own, the distribution of the lesions has been as follows: Lungs, 22; spleen, 14; kidney, 12; lymph glands, 11; liver, 11; subcutaneous tissues, 10; vertebrae, 7; ribs, 7; knee, 7; iliosacral articulation, 6; cerebrum, 6; parietal bone, 5; pleura, 4; prostate, 4; ankle, 4; metatarsals, 4; elbow, 4; pancreas, 3; blood vessel walls, 3; muscles, 3; wrist, 3; sternum, 3; cerebellum, 2; adrenal, 2; retropharyngeal and subpleural tissues, 2; myocardium, 2; pericardium, 2; meninges, 2; eye, 2; pons, 1; spinal cord, 1; spinal dura, 1; appendix, 1; colon, 1; duodenum, 1; larynx, 1; thyroid gland, 1; thyroid cartilage, 1; trachea and bronchi, 1; epididymis, 1; occipital bone, 1; metacarpal, 1; shoulder, 1; scapula, 1. The skin seems to have been involved in most of the cases reported, but some of the reports are obviously incomplete in this regard, so

9. Wade and Bel: Arch. Int. Med., 18, 1, 103-130. Rusk, G. Y.: Proc. New York Path. Soc., 1910-11, x, 48. Rusk, G. Y., and Farnell, F. J.: Univ. Calif. Publ. Path., 1912, ii, 47. Sheperd, F. J., and Rhea, L. J.: Jour. Cutan. Dis., 1911, xxix, 588. Ravogli, A.: Lancet-Clinic, 1911, cv, 489. Hill, H. P., and Dickson, E. C.: Calif. State Jour. Med., 1914, xii, 120. LeCount, E. R.: Bull. Johns Hopkins Hosp., 1915, xxvi, 315.

that no accurate statement can be made. The organs involved predominantly are those which are also attacked by tuberculosis, with the addition of the subcutaneous tissues and the central nervous system, and in gross anatomy the lesions resemble tubercles very closely. Coupling this with the close similarity in clinical course of the two diseases, it is not surprising that they should be so frequently confused.

April 10, 1916.

EXPERIMENTAL GONOCOCCAL INFECTIONS

A PRELIMINARY REPORT

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(From the Department of Experimental Medicine, University of Illinois, Chicago)

Through lack of sufficient convincing experimental evidence to the contrary, the gonococcus must still be considered a strictly human parasite.

Since its successful artificial cultivation there have been numerous attempts to produce infection in animals, both by injecting the organisms into the blood stream and by local applications or injections. They all have given doubtful or negative results. At the present time it can be said apparently without reservation that gonococcal infections in animals in the sense that the micro-organisms invade and increase within their bodies, have not been produced; but that certain tissue changes have been brought about by the toxic action of the readily autolized organisms.

There are two apparent conditions which protect experimental animals from actual gonococcal infections. The optimum temperature for growth of the gonococcus is 36 C. and unless the organism gradually becomes adapted to higher temperatures, it is readily killed at 39 C.-40 C., the normal temperature of experimental animals. Also the serum of these animals is highly bactericidal for the gonococcus. Until these protective mechanisms of these animals

have been disturbed, or the resistance of the micro-organisms has been raised against these protective conditions, it seems reasonable to assume that infection will not take place.

Danyz[1] working with anthrax bacilli found that the serum of rats is bactericidal for these organisms; but by growing the organisms on rat serum broth they grew in more and more concentrated serum. A similar resistance can be produced against arsenic by this bacillus.

It had been impossible to readily produce a typhoid carrier state in rabbits until Gay and Claypole[2] grew the organisms on rabbit serum media, when the condition could be regularly produced.

The bactericidal power of rabbit serum for the gonococcus varies with different animals and with the same animal at different seasons. However, the animals tested and used constantly in these experiments gave a bactericidal titer of 1:75 for two different strains.

Strain No. 1 was transplanted successively on rabbit blood agar and human blood agar, and the resistance was tested for each from time to time with different dilutions of fresh rabbit serum bouillon. After the fifteenth transplant it was found that those organisms grown on human blood agar were killed in dilutions of 1:64 after a forty minute exposure; while those from rabbit blood agar were still present but not increasing in a 1:32 dilution of rabbit serum after a five hour exposure.

By transplanting further, a gonococcus was grown which on the twenty-sixth transplant on rabbit media would grow readily in fresh rabbit serum 1:6 with broth.

Another strain No. 2 was grown in fresh rabbit serum broth 1:100. By four transplants on more concentrated serum an organism was secured which readily grew in fresh rabbit serum 1:4, while a similar organism grown on human serum broth was killed in a 1:64 dilution of fresh rabbit serum in twenty-four

1. Annales de l'Institut Pasteur, 1900, Vol. 14, p. 641.
2. Arch. of Intern. Med., 1913, Vol. 12, p. 613.

hours. By checking this experiment with fresh human serum it was found that the organism grown on human media yields a better growth and a growth in a greater concentration of human serum than those from rabbit media.

This adaptation on the part of the gonococci may imply not only an increased ability to meet altered cultural conditions, but the actual acquisition of greater invasive powers with which to meet the particular defenses opposed to it by the given animal. So from time to time injections have been made intravenously into rabbits. In one instance a positive blood culture was secured five days after the injection, while organisms have been found alive in the blood on the third day in many instances. Using gonococci from other media it is very unusual to get a positive blood culture after twenty-four hours.

One animal developed what was clinically a definite iritis, thirty-six hours after inoculation. Puncture of the eye and culture produced an organism similar morphologically and in staining qualities to the one inoculated. However, it grew poorly and did not withstand transplanting.

Many other animals similarly inoculated have as yet given no noticeable lesions.

By carrying these transplants further it is hoped that an organism may be secured which will regularly cause infection in rabbits.

April 10, 1916.

STREPTOTHRIX IN BRONCHOPNEUMONIA OF RATS SIMILAR TO THAT IN RAT-BITE FEVER

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Bronchopneumonia is frequent in the white rat, and occurs also in the gray rat. In the course of a study of this condition, especially as it occurs in the white rat, a streptothrix was found which may be of interest in connection with rat-bite fever in man.

Sixty white rats showing acute or chronic bronchopneumonia have been examined. A long, fine, straight or wavy filamentous organism was observed in smear preparations or by dark field illumination in fifty-six. Three lesions in which no organisms were seen were chronic. The organisms are most abundant in acute lesions. It is a gram-positive organism and stains fairly distinctly with carbol-gentian-violet and the Giemsa stain. It is distinguished from cilia by its greater length, more pointed ends and its occasional wavy form. In the dark field I have observed once or twice a slow wormlike motion, and one organism showed a corkscrew motion. They are barely visible in the tissues stained with methylene blue, but are distinct in tissues impregnated with silver nitrate according to Levaditi's method. Here, they appear more wavy and more fragmented than in other preparations. These organisms were not observed in twenty-four normal rats.

A streptothrix resembling these organisms was cultivated from twenty rats, and isolated in pure culture thirteen times. Cultures from thirty-three rats remained sterile. Why successful cultures were obtained from some rats and not from others is undetermined. The character of the lesion does not seem to make any difference. Successful cultures were more frequent in the case of sick rats and from lesions in which other bacteria were present. The other organisms isolated from twenty-two rats were *Streptococcus viridans* and *pyogenes,* pneumococcus, staphylococcus, diphtheroid bacilli, anaerobic spirilla, and a profusely growing gram-negative bacillus which was probably a contamination. Seven of these were isolated from cultures in which the streptothrix did not grow. Successful cultures were grown on human blood agar or ascites-goat-blood-agar. The various mediums for growing spirochetes were used, but no spirochetes were cultivated. This streptothrix is a facultative anaerobe, growing best at 37 C. (98.6 F.). Slight growth appears at room temperature after several days' incubation. Growth generally appears in from forty-eight to seventy-two hours as discrete,

colorless or grayish pin-point colonies. At first they appear dull, but later become glistening and increase slightly in size. The medium is not changed. The growth in the fluid of condensation and in ascites broth is white and flocculent, the medium remaining clear. The growth on Loeffler's blood serum is similar to the growth on blood agar, but does not always occur. There is no growth on plain and dextrose agar, ascites dextrose agar, in plain and dextrose broth or in milk.

In cultures the organism is slender, branching, straight or wavy, filamentous, varying greatly in length and showing bacillus and coccuslike forms. True branching is seen in young cultures, but is not especially frequent. They often show spindle or irregular shaped swellings. Twisted and wavy forms are more frequent on solid mediums than in ascites broth, where they appear generally as long threads or chains of bacilli. They do not show a radial arrangement at the periphery of the colony. They stain with ordinary stains. They are gram-negative, except the swellings, and are not acid fast. The organism here is nonmotile.

An increase in opsonins and agglutinins for this organism has been observed in infected rats.

Young, healthy rats injected intraperitoneally with cultures show acute lesions in the lungs. The organism has been isolated in pure culture from the heart's blood and lung.

This streptothrix appears to be the same as *Streptothrix muris ratti* isolated in pure culture from the blood of patients with rat-bite fever by Schottmüller[1] and Blake,[2] and seen in the blood during the paroxysms by Tileston.[3] Futaki[4] and his associates describe a motile spirochete in the skin and lymph node of two cases of rat-bite fever, but details of experiments and cultures are not available. Some of the spiral forms in my Levaditi specimens closely resemble the spirochetes shown in their drawing. Rats causing rat-bite fever have not been examined as far as known. I

1. Schottmüller: Dermat. Wchnschr., 1914, lviii, Suppl., p. 77.
2. Blake: Jour. Exper. Med., 1916, xxiii, 39.
3. Tileston, Wilder: The Etiology and Treatment of Rat-Bite Fever, The Journal A. M. A., April 1, 1916, p. 995.
4. Futaki: Jour. Exper. Med., 1916, xxiii, 249.

have examined twenty-eight wild rats, and found one infected. The lesions in the lung were the same as those observed in the white rats, and showed the same organism. As the trachea of infected rats is full of mucus containing large numbers of the organisms, it is readily seen that a bite from such a rat might be infectious.

April 10, 1916.

OBSERVATIONS ON PULMONARY INFECTION IN RATS

LUDVIG HEKTOEN

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The lesions of the lungs of rats from which the streptothrix described by Tunnicliff[1] has been obtained are essentially of the nature of purulent or mucopurulent bronchitis and bronchopneumonia. Appearances vary greatly according to the extent and stage of the process, which may be associated with suppuration, mucoid degeneration, collapse of lung tissue, and fibrous changes, all in varying degrees. The lesions are practically always multiple and may involve any part of the lung; in our material the lobe that is situated below the heart was affected oftener than any other part.

Two main types of lesions may be distinguished. In the one the affected tissue, most often part or parts of one or more lobes, is solid and red, usually with more or less well-marked nodular areas of reddish-yellow or yellowish color; on the cut surface and in the microscopic sections such areas correspond with accumulations of exudate, which is mostly cellular, within the bronchial system, and in the earlier stages the consolidation of the lung tissue proper is due to cellular exudate in the alveoli with congestion associated with collapse. This is probably the more common lesion. In a few instances an entire lobe is found uniformly solid throughout, deeply congested and red

1. Jour. Am. Med. Assn., 1916, 66, p. 1605.

or reddish-gray in color; rarely we have found more or less uniform congestion in one or more lobes with much mucus in the bronchi. In what may well be later stages of the bronchopneumonic process, the lungs are found "riddled with abscesses" with thick yellow pus; some of these appear to lie in bronchial dilatations, while others may have dense fibrous capsules.

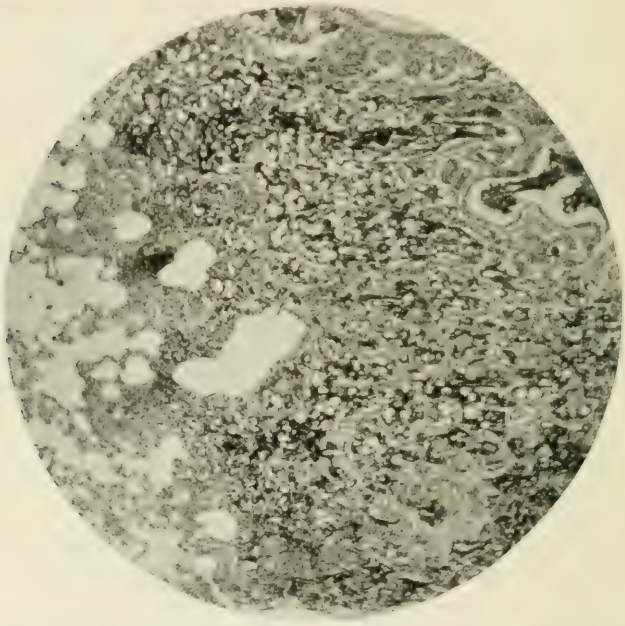

Fig. 1.—Junction of normal lung tissue and area of bronchopneumonia with mucoid changes in exudate and connective-tissue proliferation. The deeply stained material enclosing empty spaces is mucus. × 65.

In the second type of lesion districts of lung tissue, frequently with sharp but irregular margins, appear somewhat gelatinous, largely homogeneous, even semi-translucent, light-gray or reddish-gray, though often with more opaque yellowish spots. The gelatinous appearance corresponds with mucoid degeneration of the bronchopneumonic exudate, and it may be asso-

ciated with connective-tissue proliferation, the mucoid material then usually appearing dense and inspissated.

These two main types of lesions may be present in the same lungs and in the same lobe, and individual lesions occur which appear to partake of the characteristics of each type. The difference between the two types would seem to depend on the predominance of suppuration in the one and of mucoid change in the other.

As a rule in well-marked cases the bronchi and the trachea contain much turbid, viscid mucus.

Special mention must be made of certain sharply defined, solid, deeply red areas, usually at the tips of lobes, which look very much like red infarcts, but are caused apparently by collapse of lung tissue due to occlusion of bronchi either by exudate or through fibrous obliteration. Then there are pure vesicle-like lesions, usually minute, subpleural as well as deep, with clear, colorless mucoid contents, apparently formed by accumulation of mucus and mucoid material in bronchi and other spaces.

Usually the pleura is free and smooth; over large chronic abscesses there may be adhesions; occasionally scars are found and deposits of coal dust occur.

In uncomplicated cases the other organs of the body may be quite normal.

These observations concern white rats under laboratory conditions. That similar lesions occur in wild rats is shown by the following instance, the first one encountered in twenty-eight rats examined for such lesions.

Large Female Gray Rat.—The lobe under the heart is partly consolidated, with opaque, grayish, and less dense gelatinous areas; on the cut surface are spaces with a thick, viscid, grayish fluid. Discrete areas of the same nature in the left lung; in the right lung, no changes.

Microscopically the air spaces and bronchi are filled to distention with a material that stains deep-blue with hematoxylin and forms a network of finer threads and sheets, in which are entangled cells and cellular fragments, and which also contains many empty spaces; in some areas there is less of this material, but much denser accumulations of cells, mostly polymorphonuclears; in other places granulation tissue

is beginning to develop in the alveolar walls and the peribronchial tissues.

The streptothrix described by Tunnicliff was found in the lungs of this rat.

The obvious symptoms in the more or less severely affected rat are lack of energy, standstill or loss of weight, ruffled hair, and failure to maintain the usual degree of cleanliness. Death may occur after a variable time, sometimes weeks, but in many cases complete recovery appears to take place. No doubt many so-called "stunts" or "runts," rats that do not thrive or grow, are examples of chronic pulmonary infections.

Mild forms of pulmonary disease may be present in rats that seem to be in good health, undoubtedly to a much larger extent than is now generally known. The infection known as rat typhoid and the infections or infection now under consideration sometimes occur together, and according to our experience the death rate of such mixed infection is high.

Further studies will be made with special reference to the causative relations of the streptothrix present so commonly in these pulmonary lesions of rats.

April 10, 1916.

SPONTANEOUS SARCOMA IN MICE

MAUD SLYE, HARRIET F. HOLMES

AND

H. GIDEON WELLS

(From the Otho S. A. Sprague Memorial Institute and the University of Chicago)

In a series of 12,000 autopsies on the bodies of mice dying at all ages, either from natural causes or in a relatively small proportion from accident, there were found eighty-seven mice with neoplasms meeting all the criteria of sarcoma. These do not include any growths of the character of lymphosarcomas, because of the recognized uncertainty of the nature and diagnosis of these neoplasms; also we have excluded eleven cases of characteristic mediastinal lymphoid tumors,

arising at the site of the thymus and infiltrating the lungs. Tumors of the testicle, adrenal, ovaries and kidneys of "mesothelioma" character have also been omitted.

Spindle cell sarcomas constitute over half the tumors, there being 47 of all types, not including 3 oval celled, 3 perivascular sarcomas and two alveolar sarcomas. There were 12 osteoid sarcomas, 10 polymorphous cell, and 10 round cell sarcomas. Metastasis was observed in 23 cases, or 26.4 per cent., the osteoid sarcomas leading with 75 per cent., and only 13 per cent. in the spindle cell sarcomas. Lungs, liver and lymph glands showed most of the metastases. In all respects these sarcomas of mice correspond with the sarcomas of men, although we have found no examples of melanosarcoma, multiple myelomas or myeloid sarcoma. In at least eleven cases the sarcomas definitely arose at the site of previous injuries. In a few instances there seemed to be two distinct primary sarcomas in the same mouse, and there were three instances in which the growths suggested a mixture of sarcomatous and carcinomatous elements. About half the sarcomas arose in the subcutaneous tissues, apparently from the mammary gland in most cases; and next in frequency from the osseous tissues. Two cases of sarcoma of the uterus were observed, the only uterine tumors of any kind observed in all the autopsies. Twenty of the sarcoma mice also had other independent tumors, lung tumors being most numerous. Two mammary gland tumors were found closely resembling in structure the embryonal adenosarcoma of the kidney of man and other animals, but without renal involvement. The influence of inheritance on the incidence of sarcoma has been found to be marked, but is reserved for further discussion.

May 1, 1916.

Note.—The full report of these observations will appear in the Joural of Cancer Research.

PERITHELIOMA OF HYPOPHYSIS

WITH REPORT OF A CASE

HARRY JACKSON

Of all the reported tumors occurring in the hypophysis that of perithelioma is the rarest. Only one undoubted case has been reported.[1] Five cases of perithelial angiosarcoma have been reported by various authors, but no one of these has all the typical characteristics of the cases reported by Kon and myself. Following is a brief description of a tumor, diagnosticated as perithelioma, the full discussion of which will appear with that of the other hypophysial tumors in a forthcoming number of *Surgery, Gynecology and Obstetrics.*

The tumor occurred in a girl 12 years of age, on the service of Dr. A. B. Kanavel. The patient suffered from gradually increasing blindness. The examination of the body was negative except for the tumor of the brain.

The brain was compressed by a tumor the size of a goose egg which lay at the base of the brain, taking its origin from the region of the hypophysis. The sella was slightly eroded and somewhat enlarged. Most of the tumor had grown up out of the sella and had pressed the brain upward, forward and backward as well as laterally. On sagittal section, the floor of the third ventricle is seen to be raised and the lateral ventricles encroached on. The corpus callosum is thinned as are the optic tracts which are stretched like a ribbon over the surface of the advancing tumor. The cranial nerves (third to eighth) are pressed on. Posteriorly the tumor has pushed the pons and medulla backward and downward so that they lie at a right angle to the cerebrum.

The tumor is a well circumscribed oval mass covered with a thick capsule and measures 7 by 5.5 by 4 cm. It extends from the frontal lobes to the pons, growing laterally against the cerebral peduncles and temporal lobes. On cut section, the anterior and upper portions appear grayish-red in color and friable. The posterior and inferior portions are grayish in color and the consistency somewhat firmer than brain sub-

1. Kon: Rare Tumors of the Hypophysis, Beitrage z. Path. Anat. u. Allg. Path., 44, 1908, p. 249.

stance. The capsule in places measures 3 to 4 mm. in thickness. No trace of the hypophysis is seen.

Microscopically, sections taken from the reddish areas show large numbers of blood sinuses, some of which appear to anastomose with each other (Fig. 1). The vessels lie in a matrix of embryonic cells, which however, are everywhere separated from the blood vessels by a clear space of considerable thickness within which are discernible a few connective tissue fibers and lymphocytes. The inner lining of

Fig. 1.—Perithelioma of hypophysis, × 110.

this space is the intima of the blood vessel. The outer lining forms the edge of the matrix of embryonic cells. This matrix is composed of moderately large round or oval cells, the nuclei of which are round and deeply staining. The nucleus occupies about one half the cell, surrounding which is a clear, vacuolated cytoplasm. The cells are closely packed together, and nowhere do they penetrate the clear zone about the blood vessels. In some sections they are radially arranged about the blood vessel, in other sections concentrically. In

the grayish portion of the tumor, the blood vessels are not so numerous or large, but the embryonic cells are larger. The capsule is infiltrated with round cells and columns of tumor cells.

The diagnosis of perithelioma is based on the presence of a well defined perivascular space about the abundant blood vessels and the characteristic endothelial cells of the tumor mass. It closely resembles the description given by Kon who found no other case like his in the literature.

May 1, 1916.

TRANSACTIONS OF THE CHICAGO PATHOLOGICAL SOCIETY

VOL. X. JANUARY 1, 1917. NO. 4.

BACTERIOLOGY AND THE MEDICAL CURRICULUM

PRESIDENTIAL ADDRESS

ARTHUR I. KENDALL

The object of this discussion is to present, as fully as the very brief time available will permit, a few of the difficulties which confront the teacher who attempts to impart adequately the many aspects of Medical Bacteriology, and to consider equally briefly the possibilities whereby the situation may be amended.

Bacteriology, and its highly specialized offspring immunology, is a science that fills a somewhat unique position in a modern medical curriculum. Its earlier history is intimately associated with pathology and this ancillary position remained unquestioned until a recognition of the importance of microbic participation in a vast field of human activity, the rapid growth of the entire field of parasitology and the elucidation of coexistent reciprocal relations between host and parasite focused attention upon the magnitude of the subject. The extent to which bacterial literature has accumulated during the last three decades and the wonderful developments in the domain of experimental pathology appear to furnish unequivocal evidence in favor of the view that one teacher can hardly keep abreast of the progress in both pathology and bacteriology and justly present their respective claims.

The rise and development of the so-called laboratory branches of medicine during the last quarter century

is eloquent testimony to the gradual change which has taken place in the theory underlying the practice of medicine; it marks the transition from empiricism based upon experience to fact founded upon adequately controlled experiment — the metamorphosis of the science of medicine, in other words. It is but natural that bacteriology, the youngest of these medical sciences, should have received less recognition and less representation in the curriculum of medicine than older branches even though the relation of bacteria to medicine is so obvious. The rapid and extensive developments in this branch, spectacular and epoch-making as they undoubtedly are, are not unique — the entire field of medicine is seething with new and important discoveries gleaned not only from this angle but from older and better established subjects as well. Thus pathology is forging ahead through at least three principal channels, which of course possess numerous collateral branches, namely, morbid anatomy, morbid function or morbid physiology, and morbid chemistry. The frontiers of all these sciences merge almost imperceptibly and those of pathology and bacteriology overlap through the field of pathogenic bacteria; in other respects bacteriology is quite an independent subject concerned not alone with a host but with the study of microbes which react with a host as well.

The self-imposed limitations of this discussion do not permit of a presentation here of the claims of bacteria to recognition other than of those pathogenic micro-organisms whose activities are in partial opposition to the well-being of man — the pathogenic bacteria, in other words. This is medical bacteriology.

Medical bacteriology, broadly speaking, involves a consideration of parasitic and pathogenic bacteria together with those complex reciprocal relations between host and parasite which comprise the phenomena of immunology. It brings together through the toxins, enzymes and other products of microbic activity the fields of physics and chemistry because bacteria in the last analysis are living chemical agents which possess interest and importance "Not for what they are, but for what they do, since our interest cen-

ters in the host rather than the parasite," as Theobald Smith has so admirably stated. This dynamic conception of bacteria will inevitably supplant to a large degree the older static, botanical, or anatomical point of view precisely as the study of the dynamics of man have so largely supplanted the purely anatomic aspect of the human mechanism. This does not mean that the anatomic basis for the vital activities of man or microbe will ever be relegated to an unimportant or secondary place; it does indicate the undeniable determination of investigators to examine the forces which actuate anatomic entities.

The dynamic study of bacteria, which will play a most important part in the future development of the subject, will impose an additional burden upon an already overloaded curriculum. Even at the present time the space allotted to bacteriology, usually from 96 to 160 hours, is quite inadequate and the future legitimate demands for additional time cannot be postponed indefinitely. It is important, therefore, to take an inventory, as it were, of the present status and to formulate tentative plans for the future, bearing in mind, of course, that a majority if not all medical subjects will require future readjustment as well.

The present problem confronting teachers in bacteriology is to present in some detail to the student coherent progressive theoretical information and practical acquaintance with the anatomy, physiology and chemistry of bacteria, the essential features of their parisitism and pathogenism and the nature and extent of the respective defensive and offensive weapons of the host and parasite which collectively comprise immunology. In addition the student must be taught the prominent characteristics of a considerable number of microbes with the dual objective of indicating their relation to disease and the prevention of disease incited by them. Finally practical methods of bacterial diagnosis, which include not only cultural and serologic examinations but animal experimentation as well, must be studied. This implies not only the actual handling of bacteria, viewing whenever possible the naturally acquired and experimentally induced disease peculiar to each type,

it requires the individual testing of the various reactions whereby diagnosis, prognosis and even specific treatment are arrived at.

A majority of medical students come to bacteriology quite unfamiliar with the somewhat unusual nature of the subject and the earlier exercises almost of necessity are arranged to develop a technic sufficiently perfect to minimize mutual accidents to teacher and pupil. The acquisition of this technic is onerous and time-consuming. When the student exhibits sufficient dexterity to warrant the presentation of the more formidable bacteria and has mastered the essential elements of morphologic and cultural technic the term is well under way and the residual time is materially lessened. It is perfectly obvious that precious time has been expended in hurriedly acquiring a rough working knowledge of the mechanics of the subject.

In this respect alone bacteriology in comparison with other laboratory subjects is at an obvious disadvantage. Whenever the acquisition of technic is an important feature in other subjects the time allowance in the medical curriculum or prescribed premedical study relieves the situation in no inconsiderable degree.

Enough has been said to make it obvious that bacteriology like many other medical subjects is allotted insufficient time for its presentation. The acute problem for solution is to obtain more time. The medical schedule is so crowded at the time bacteriology is offered that material relief through an extension of hours would scarcely be feasible. Two possibilities, however, present themselves — to require at least a minimal amount of general bacteriology including the routine of media making, staining and general cultural methods in the premedical years, or to extend somewhat the customary domain of clinical diagnosis and introduce there the more detailed aspects of the subject, including an intensive study of the more important immunologic reactions, the theory and practice of vaccine therapy, and special diagnostic methods. Special individual interest in bacteriology would rather naturally lead the student to elect an advanced research course in the senior year. Here the more complex

procedures including the highly specialized method of complement fixation could advantageously be pursued. A thorough consideration of the subject matter of such an advanced course could hardly be regarded as practicable for introduction into the more elementary courses since the preparation and standardization of the reagents alone is almost an art in itself.

The first possibility has much in its favor even though it may require a readjustment of premedical courses. The general educational advantages which would flow from a well-arranged course of study in general bacteriology with particular emphasis laid upon the relation of micro-organisms to the many problems of every-day life of the individual, the community and the state need little comment. The ever-widening scope of discussions relating to individual and civic health in the daily press presuppose at least a familiarity with bacterial terminology, and they make for a better realization of the mutual interdependence of individuals in communal existence. Firsthand knowledge of the general principles of bacteriology (which would necessitate the acquisition of bacteriologic technic) would not only logically promote interest in the general hygienic movements so necessary for the public welfare, it would leave in the restricted field under discussion, the limited available time assigned to bacteriology in the medical school curriculum practically intact for the consideration of the purely medical aspects of the subject.

The second alternative, an extension of time in the course in clinical diagnosis to be devoted to bacteriology along the lines indicated above would also appear to possess some advantages. The student in this period of development would undoubtedly possess a broader viewpoint of the relation of bacteria to medicine and in this respect a distinct advance might be made over the prevailing practice. On the other hand, it is on the whole poor pedagogy to attempt to drill the student in elementary and fundamental laboratory practice in the clinical years where the application rather than the acquisition of laboratory technic is advantageously taught. Indeed, at this period of the

student's career he should be able, under proper supervision, to make the necessary serologic and bacteriologic examinations himself. The problem of available time is again the deterring factor, however, and the final and satisfactory solution would appear to rest upon a careful revaluation of the entire medical curriculum, including the premedical requirements, with a possible redistribution of time allotted to all medical subjects, based upon their present and prospective importance in medicine.

Oct. 9, 1916.

TWO CASES OF TUMOR OF THE OCCIPITAL LOBE

PETER BASSOE

Case 1.—A man, 40 years old, was first seen by the writer on March 29, 1915. For two years he had suffered from severe headache, which at first came on once a month and gradually became more frequent. During these attacks the headache was general. For some months he also had some dull occipital pain in the interval and a sensation as if the ear-drums were being pushed out. Sometimes he had a sensation as if "the nerves were being drilled into on the right side of the head." His vision had been failing for about six weeks and he had vomited on several occasions.

Examination.—Bilateral papillitis. With the right eye he could only read headlines in a newspaper, but he could read ordinary print with the left one. Form fields not materially narrowed. He habitually kept the head backward and rotated to the right. No nystagmus or ocular palsy. Corneal reflex normal. Hearing and smell normal. No paralysis or sensory disturbance. Tendon and superficial reflexes normal.

One week later the patient entered the surgical service of Dr. Bevan in the Presbyterian Hospital. Lumbar puncture revealed a perfectly normal spinal fluid except for a weakly positive Nonne globulin test, and a slight reaction in the higher dilutions with the Lange gold test. A subtemporal decompressive operation was performed on April 8. Soon after the operation he developed left homonymous hemianopsia, diminished sensation in the left arm and the left side of the face, with some subjective numbness in the left arm. Left ankle clonus appeared. A large cerebral hernia formed.

Gradually the entire left side became anesthetic. For a time the papillitis receded somewhat and the headache was less marked, but it returned after some months and morning vomiting again appeared. On Jan. 11, 1916, the hernia was tapped with relief for a few days. On January 21 Dr. E. V. L. Brown reported bilateral papillitis, mainly in the nasal halves with swelling of 4 D. in the right eye and slightly more in the left eye. As a posterior fossa tumor was suspected, a sub-occipital operation in two stages was advised. The bone was removed on January 24 and the dura opened and cerebellum explored ten days later. No lesion was found. The patient

Fig. 1, Case 1.—Right cerebral hemisphere showing tumor infiltration of pia.

went home and died on March 3, 1916. Only the brain was examined at the necropsy, which was performed by Dr. B. O. Raulston, who kindly placed the brain at my disposal.

Description of Gross Specimen.—The dura is adherent over a large part of the right occipital and parietal lobes; also adherent for a distance of about 2 cm. on the mesial surface at the occipito-parietal junction. One cm. to the right of the median line is a crater-shaped depression, the center of which is 5.5 cm. above the occipital pole. Here the dura is thicker and more firmly adherent than elsewhere. The overlying bone shows a localized thickening fitting exactly into the depression described. The greatest thickness of bone at the depression is 3 cm. The dura can be peeled

fairly easily in the crater-shaped depression. On cutting the falx cerebri it is found that the superior longitudinal sinus for a distance of 6 cm. from the posterior end is filled by a firm, white, adherent, and apparently vascularized tissue (Fig. 3) which ends free as a rounded, smooth prominence in the torcular herophili. On the mesial surface opposite the crater described is a whitish growth measuring 3.5 cm. along the sinus, 1.2 cm. from above downward and less than 1 mm. in thickness.

After separating the dura it is seen that the pia arachnoid of the entire right parietal lobe and the anterior part of the

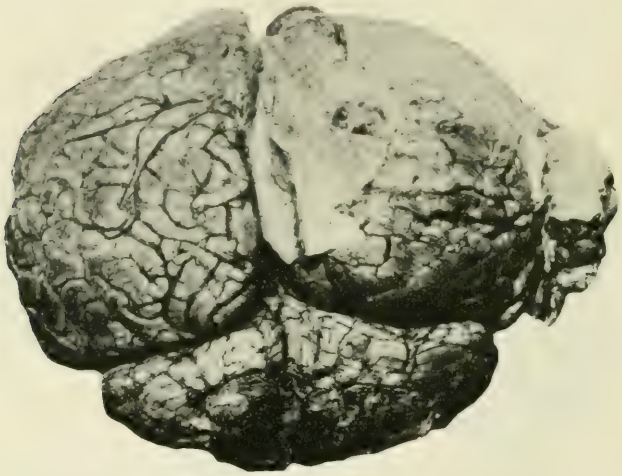

Fig. 2, Case 1.—Posterior view of brain showing infiltration of pia, adhesion, and tumor infiltration of dura in region of torcular, and the hernia.

occipital lobe, and the superior part of the temporal lobe is infiltrated by a grayish-white tumor growth which completely covers and obliterates all sulci and gyri (Fig. 1). The tumor extends within 1 cm. of a cerebral hernia existing in the right temporal region as the result of a decompressive operation (Figs. 2 and 4). The anterior border of the tumor is practically at the fissure of Rolando.

There is a partly necrotic herniated mass at both cerebellar poles, also the result of a surgical operation. There is considerable whitish thickening of the pia on both sides of this median fissure in the region of the motor area. The pia at the base is smooth.

The greatest width of the left cerebral hemisphere is 7 cm.; that of the right, exclusive of the temporal hernia, is 8.5 cm.

The upper part of the pons is largely displaced to the left side by the formation of a liplike protrusion of the under surface of the right hemisphere.

On sectioning the brain it is found that the tumor begins posteriorly at the occipital pole and extends forward, gradually increasing in size. It is intimately connected with the dura and the plugged superior longitudinal sinus, especially posteriorly. In Figure 4 we see a partial demarcation between

Fig. 3, Case 1.—Detached dura showing section of superior longitudinal sinus filled with tumor.

the tumor in the interior and that spreading out on the upper surface; a narrow zone of brain tissue is seen to separate them. In this section we also see the cerebral hernia caused by the first operation and the cystic condition in the vicinity, evidently the result of traumatic softening. The tumor in the interior ends quite abruptly 1 cm. in front of this section, while the meningeal infiltration extends to the Rolandic fissure (see Fig. 1). The anteroposterior dimension of the tumor is 10 cm.—the greatest width is 7.5 cm.

Histological Examination.—Both the tumor in the occipital lobe and that filling the sinus show typical structure of

hemangio-endothelioma, the tendency to concentric arrangement of the cells being very marked (Fig. 5).

Case 2.—A man, 55 years old, was first seen on Aug. 5, 1915. He gave no history of venereal disease and no other previous disease of importance, having merely had a few attacks of "grippe" and lumbago and had been subject to headaches since youth. He was a printer and early in 1915 he noticed that he had some difficulty in locating the boxes of type and particularly that he did not seem to see so well to the left, so he frequently would omit the first letter of a word. When reading, whole words would sometimes seem replaced by blank spaces. In February he consulted Dr. W. H. Wilder who kindly informed me that there was no marked

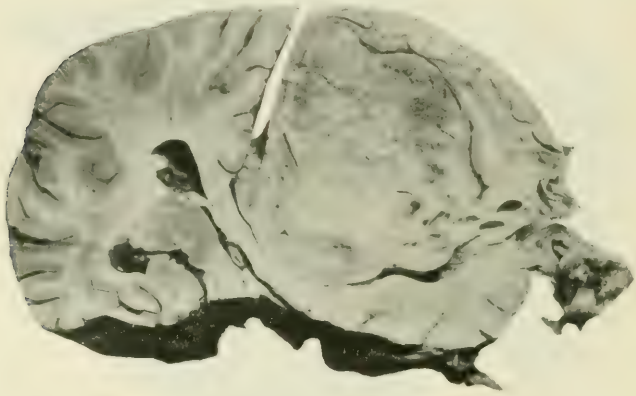

Fig. 4, Case 1.—7 cm. in front of occipital pole showing tumor in interior and along surface. Also hernia and necrosis and vacuolation about sinus leading to same.

contraction of the fields but a scotoma was present. With correction vision was $^{20}/_{20}$. The fundi were normal except for arteriosclerotic changes. At this time he also developed nearly constant headache, chiefly in the right frontal region. This gradually grew more severe and kept him awake nights. By the middle of March weakness and clumsiness in the left arm and leg became apparent and gradually increased. In July vomiting became frequent. In April there was retention of urine for a few days and the prostate gland was found to be enlarged. A Wassermann test with the blood at this time was negative. From April on incontinence of urine and feces was the rule; he became forgetful and at times confused. No convulsions or speech disturbance at any time. The chief

findings were: left hemianopsia and partial left hemiplegia; the left abdominal reflex was absent, right present; both knee jerks were increased; ankle and plantar reflexes equal and normal. The patient came to the Presbyterian Hospital on August 9. Examination of the eye by Dr. C. G. Darling revealed marked bilateral papillitis, swelling of left disk 4 D., right disk 2 D. R. V. $^{20}/_{25}$ — 3; L. V. $^{20}/_{20}$ — 2. Blood pressure 125. Wassermann test with the blood negative, with spinal fluid positive. The latter gave a strongly positive

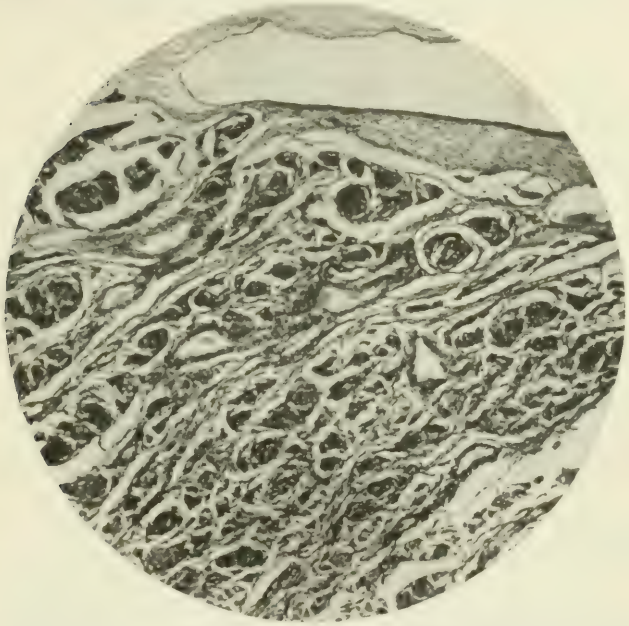

Fig. 5, Case 1.—Photomicrograph of tumor filling superior longitudinal sinus in its posterior portion.

Nonne-Apelt test and cytologic examination revealed 33 large mononuclear cells and eight lymphocytes per cubic millimeter. The Lange gold test gave a reaction as follows (Maximum reaction recorded as 5): 0, 0, 0, 1, 2, 2, 2, 1, 0, 0. This reaction is both too weak and too far to the right to be suggestive of syphilis. The urine contained a trace of albumin, occasional granular casts and leukocytes. The patient rapidly grew worse and examination of sensation could not be made. He

vomited very frequently and later developed hiccough. The last four days of his life the temperature gradually rose, reaching 106.4 degrees just before death on August 16.

Only the brain was examined postmortem.

The dura over the right occipital lobe on its outer surface and at the pole is adherent and slightly thickened. It can be readily separated without tearing the pia-arachnoid. The latter has a peculiar puckered appearance with only slight thickening but obliteration of the normal surface markings over the occipital pole and the external surface of the occipital lobe and adjacent part of the temporal lobe (Fig. 6). On

Fig. 6, Case 2.—Lateral view showing pial infiltration (carcinomatous).

section a tumor growth is found to extend from the occipital pole forward to within 4 cm. of the tip of the temporal lobe. The greatest width of the tumor is 2 cm. in front of the occipital pole where it measures 5 by 6 cm., and occupies the external and inferior two thirds of the vertical section. The lowest part of the mesial surface is involved for a distance of 3 cm., from the pole but not more anteriorly. The calcarine fissure is involved only at its extreme posterior end. The tumor gradually tapers anteriorly and remains close to the external surface. It is distinctly infiltrating and is the seat of several hemorrhages the largest of which is near the anterior end and measures 20 by 5 mm. The posterior horn

of the lateral ventricle is collapsed on the right side. Histologic examination shows the tumor to be a papillary carcinoma, hence metastatic. The primary site is doubtful, possibly the prostate.

Oct. 9, 1916.

THE SPECIFICITY OF THE ABDERHALDEN REACTION WITH VEGETABLE PROTEIN *

OSCAR J. ELSESSER

(Abstract)

The action of immune sera on purified vegetable proteins as determined by the Abderhalden reaction seems to be only quantitatively specific. Immune sera tend to react more often and more strongly with their specific substrates than with any other substrate. However, the reaction is far from being absolutely specific.

An immune serum may or may not react specifically with its own antigen; in the same test it may not react at all with its antigen, while reacting with other proteins.

Immune sera against closely allied proteins tend to interact with these various antigens. This is especially demonstrated by the interreactions among the proteins from the leguminous seeds.

A greater degree of specificity exists between animal proteins (egg white) and vegetable proteins than between different vegetable proteins.

The serum of an immune rabbit is not constant in its reactive power over a continued period, nor in the degree of specificity it exhibits. There also exists an apparent difference between the sera of the individual rabbits in these regards.

It is demonstrated in this work that the specificity of the Abderhalden reaction (dialysis method) in experimental animals (rabbits) immunized with pure isolated vegetable proteins is far from being absolute. The conditions under which this experimental work

* The full details are published in The Journal of Infectious Diseases November, 1916.

was performed were rigidly controlled and the requisite care was constantly exercised in performing all the Abderhalden tests. The biologic interrelationship and specificity of the preparations of vegetable proteins used for this work have been previously tested by means of anaphylaxis, complement-fixation, and precipitin reactions.

Under the conditions of the experiments the Abderhalden reaction is at best only quantitatively specific and even this quanitative specificity is not always exhibited. This is demonstrated by the following observations: (1) an homologous substrate may react specifically with its immune serum, no other protein reacting; (2) it may vary quantitatively in the degree of interreaction with its own immune serum; (3) it may react with its immune serum but no more strongly than do the heterologous substrates tried against the same immune serum; (4) it may give no reaction against its immune serum, while other heterologous proteins may react strongly against this serum; (5) it may react at times more strongly with a heterologous immune serum than with its own immune serum. However, there is an obvious tendency for a substrate to react more often and yield stronger reactions when tested against its homologous immune serum, than when tested against a heterologous immune serum.

When the test is made with closely allied pure vegetable proteins, the Abderhalden reaction tends to be less quantitatively specific the more similar these same proteins are. However, there is no absolute specificity even between widely diverse proteins, such as egg white and pure vegetable protein, as tested in our experiments.

In comparing the results obtained by the Abderhalden test with those obtained by anaphylaxis, by Wells, Osborne and Lake, using the same pure vegetable proteins in each case, it was found that the results present certain resemblances, but also often definite differences. In either reaction the more closely the proteins are allied chemically and physically, the less specific the reactions tend to become. On the whole, however, the results obtained by anaphylaxis are much more constant and specific.

Oct. 9, 1916.

PRIMARY CARCINOMA OF THE URETER *

E. C. SCHMITT

With the reporting of a case of primary carcinoma of the ureter observed at autopsy the cases of cancer on record limited to this particular structure were reviewed, and in all nineteen other cases were found.

The following is a brief abstract of the case in question; The patient was a woman, age 55 years. Admitted to Cook County Hospital on Aug. 24, 1915, and died Nov. 5, 1915. Necropsy was performed by Dr. H. G. Wells. Gross pathology. To the left of the median line in relation to the left kidney there was a tumor mass placed retroperitoneally firmly adherent to the vertebral column from the eleventh dorsal to the third lumbar vertebra. The mass was fluctuating and contained a purulent fluid with many shreds of necrotic tissue. The cavity measured 10 cm. in diameter and 15 cm. vertically, the wall totalling 2 to 3 cm. thick in most places. The upper boundary lay somewhat above the junction of the ureter with the pelvis of the kidney. The origin of the ureter was occluded by the cancer tissue causing a dilatation of the renal pelvis. The lower boundary was continuous with the ureter which was found extending as an occluded and solid cord 3 cm. within the necrotic cavity. Below this point, the ureter, where it makes its exit from the cavity, was normal. There was some diffuse neoplastic tissue surrounding the aorta and cava binding these vessels and the prevertebral tissue into a solid mass with the ureteral growth. The regional lymph glands did not seem to be enlarged. Secondary growths were found in the liver and in the left kidney. Microscopically the growth was diagnosed as a transitional celled carcinoma with primary origin in the ureter. Metastases were found in the portal canal of the liver, under the capsule of the left kidney and in the bodies of several vertebrae, the latter showed an invasion of the bone trabeculae by the tumor cells.

Of the twenty cases reported the sexes are equally represented. The average age was 56 years. Most of the cases were accidental findings at autopsy.

* A full report of this and previous cases reported in the literature will be found in the October, 1916, number of The Am. Jour. of Cancer Research.

Hematuria occurs almost without an exception, frequently accompanied by hydronephrosis. Pain appears late in the course of the disease and is severe and intense. Of the twenty cases, calculi were found in only four, so the etiology is obscure. Operations were performed on ten cases with a reported recovery of three and of these it was too early to state at the time reported whether there was a recurrence, though one patient was reported well one year after the operation.

Oct. 9, 1916.

DEMONSTRATION OF A LARGE SACCULAR ANEURYSM OF THE BASILAR ARTERY

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(From the Pathological Laboratory of Rush Medical College)

On March 29, 1916, a man, 53 years old, was brought to the Cook County Hospital and admitted into the service of Dr. Loeb in coma and died at the end of eight hours.

His wife said that for several months he had suffered with headaches which became extremely severe about three weeks before and that from this time he did not leave his bed. On the night before death he felt a stiffness in his feet and gradually lost consciousness which was not regained. For one week before he came to the hospital, he had been attended by a physician who made the diagnosis of arteriosclerosis and cerebral hemorrhage.

In the hospital examination revealed enlargement of the left pupil and labored respiration; this last symptom grew gradually worse until death. At the postmortem examination (Dr. E. R. Le Count) an aneurysm of the basilar artery 3.7 cm. long and 3.4 cm. wide, covering the pons and loosely adherent to it was found. It was situated 1.5 cm. more to the left and pressed deeply into the flocculus and cerebral peduncle, which structures were flattened, and their margins spread over the side of the aneurysm in the form of a thin membrane of shreds and fibers. At the base, the aneurysm was demarkated by a shallow groove in the midline, which had its origin between the vertebral arteries and extended as far as the basilar artery (Plate 1).

The oculomotor, trochlear, trigeminal, abducens, facial and acustic nerves on the left side were partially flattened as this

tumor pressed into the brain stem, forming a smooth depression about 4 mm. in depth at the center of the pons.

When a soft probe was introduced through the vertebral arteries they were both found to communicate with the basilar artery by a narrow channel along the shallow groove of the aneurysm, while in all other directions the probe encountered

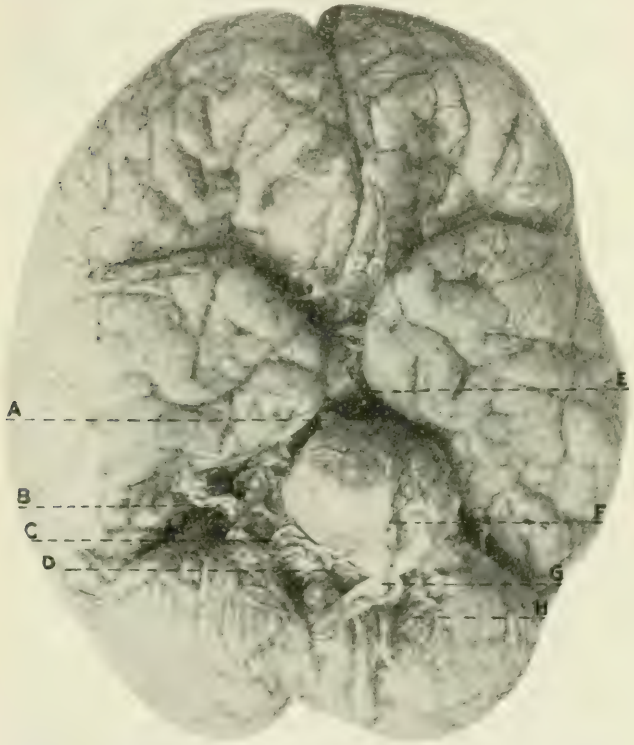

Fig. 1.—A.—A, Basilaris; B.—N, Trigeminus; C.—N, Abducens; D.—N, Facialis and Acusticus; E.—Optic chiasma; F.—Groove; G.—AA, Vertebrales; H.—Nervus Glossopharyngeus and Vagus.

resistance. When a coronal section was made through the central part of the aneurysm, it was seen to consist partly of dark brown, porous blood clots and partly of laminated bands of grayish-white older clots. The channel through which the blood had last flowed was represented by a ragged irregularly

shaped opening, about 4 mm. in diameter, more or less filled with a dark, brownish-red, soft and porous coagulate.

The wall of the sac was thickened and irregular, three times thicker toward the base, in which latter portion there were small openings running longitudinally in the substance of the wall (Plate 2).. The arteries of the base of the brain were considerably thickened and sclerosed. The cerebral convolutions were flattened, larger than normal and the sulci almost completely obliterated. The vessels of the leptomeninges were engorged and those of the Sylvian fissure were opaque. The chiasma opticum was swollen; it appeared like a cerebral convolution, forming a soft pouch, compressible and gave the impression of being filled with air. There were no other pathological changes.

Most authors agree that aneurysms of the cerebral vessels are usually met with in the internal carotid, middle cerebral or basilar artery and Lebert,[1] Wichern,[2] Wright,[3] and Apert,[4] consider that the latter is the one most frequently affected but that it is generally overlooked or that a wrong diagnosis is made because the symptoms are not at all characteristic and in a great number of patients there are no symptoms whatever until immediately before death, and then again the symptoms may be extremely variable according to the size and position of the lesion, its degree of hardness and its more or less rapid growth.

A considerable amount of work has been done and a relatively great number of cases have been collected and studied as to etiology, symptomatology, pathology and treatment and a short résumé is given here of the literature available on the subject.

According to Beadles[5] basilar aneurysms reach a large size as a rule, being from a bean to a pigeon's egg. Only a single case is known where the aneurysm reached the size of a hen's egg (Serres[6]) and five

1. Lebert: Ueber Aneurysmen der Gehirnarterien, Berl. klin. Wchnschr., 1866, xx, pp. 209, 229, 249, 281, 336, 345, 386, 402.
2. Wichern: Klin. Beiträge zur Kenntniss der Gehirnaneurysmen, Deutsch. Ztschr. f. Nervenheilkunde, Leipzig, 1912, xliv, 220-263.
3. Wright: Lancet, London, 1882, ii, 805.
4. Apert: Anévrisme de l'artère basilaire, Bulletin de la société anatomique de Paris, 1881, xxxi, 1421.
5. Beadles, Aneurysms of the larger cerebral arteries, Brain, London, 1907, xxx, p. 285.
6. Serres: Archives générales de Médecine de Paris, 1826, x, p. 421.

cases are on record only which can compare in size with the one here presented.

The symptoms, as stated above, are extremely variable according to the amount of pressure exerted on the immediate surroundings. Griesinger,[7] who collected twenty-one basilar aneurysms, says:

The aneurysm acts like a tumor; a strong, slowly growing pressure may produce a considerable atrophy of parts exposed. The immediate surrounding of the aneurysm is of course the pons, and therefore the symptoms are those characteristic to lesions of the pons.

If the fibrin and blood clot produces an obliteration of the vessels we get the corresponding symptoms due to lesion of the parts supplied by the basilar artery, f. i. the pons, which is supplied directly by small arterioles from this vessel, and

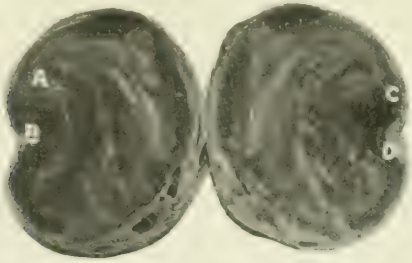

Fig. 2.—Cross-section of the basilar aneurysm in the midline. A.—Vertebral portion; B.—Lumen; C.—Basilar portion; D.—Lumen. Natural size.

the result is malnutrition, deterioration, and softening with their manifestations.

Again, according to the position, the aneurysm may press on the nerve trunk, f. i. the acusticus and facialis, if it is more toward the posterior end of the basilar artery, or the oculomotor may be involved if the seat of the aneurysm is at the anterior bifurcation.

Finally in many cases we may have a rupture with apoplectiform symptoms and death.

In other aneurysmata some clots may become detached and emboli with their manifestations be the result.

Of the symptoms due to lesions in the pons and corresponding nerves, paralysis alternans is the most characteristic fea-

7. Griesinger: Das Aneurysma der Basilar-arterie, Archiv der Heilkunde, 1862.

ture; f. i. where there is paralysis of the facialis or abducens or trigeminus on one side with paralysis of the extremities on the other side. However, there are pontical lesions where there is no paralysis alternans and where we find paraplegia and even paralysis of all the four extremities, in patients where the aneurysm occupied the midline. The symptoms therefore which will be most characteristic are those that occur rarely in other brain diseases; f. i. dysphagia, disturbances of hearing, dyspnea, difficult phonation and disturbances of urine secretion without impairment of intelligence and consciousness; further, paraplegia or paralysis of all the four extremities, paralysis alternans and the continuous sensation of knocking (klopfen) in the occipital region; the nonpresence of spontaneous epileptiform cramps and the frequent absence of sensorial symptoms. If with any of these symptoms we find arteriosclerosis or an aneurysm elsewhere, there is a strong probability of a basilar aneurysm; also if with pontical symptoms of longer duration we get an apoplectic attack and especially if the pulse of both the carotids is increased in strength.

Lebert,[8] who collected a series of thirty-one basilar aneurysms (the twenty-one of Griesinger included) also agrees that the alterations produced by the pressure on the brain stem are important factors and that the symptoms depend on the site of the aneurysm; sometimes the oculomotor may be affected, but as a rule the fifth to the tenth pair are most frequently involved. Headache and vertigo are the most constant symptoms. Mental disturbances are extremely rare. Convulsions are very rare in the early stages. Severe pains in the occipital region progressing toward the shoulder, with rigidity of the neck, a sensation of the head being drawn backward and difficulty to move the head forward, in one word, tetanic rigidity and chronic cramps belong already to the stages of apoplexy due to lesions in the pons and its proximal parts which may be produced either by pressure or rupture of the aneurysm. The rather frequent deafness is due to obliteration of the arteries which supply the inner ear and partially due to pressure on the auditory nerve at its exit. Articular speech disturbances and dysphagia are characteristic, rather frequent, and vary in severity

8. Lebert: ibid.

and constancy. Nausea and vomiting is especially frequent where rupture of the aneurysm occurs. Dyspnea occurred in five cases without any alterations in the organs of respiration. Disturbances of motion consisted in rigidity and contracture of the neck extending to the back; rigidity of the maxilla, contracture of one half of the face or part of a member. Cramps may be present and manifest themselves by rolling of the eyeballs, twitching of the face or one member or one half of the body. Hemiplegia is due to the fact that the aneurysm is placed to one side. Paraplegia occurs mostly after an attack of apoplexy. Oculomotor symptoms manifest themselves always on the opposite side of the hemiplegia.

Hey,[9] after reviewing a collection of eighty basilar aneurysms (those of Lebert included) confirms in general the latter author's findings. As the most frequent symptoms he cites dysphagia, due to pressure on the glossopharyngeus; articulatory difficulties, dysarthry and anarthry up to complete aphonia, due to involvement of vagus and hypoglossus; dyspnea and Cheyne-Stokes breathing; intermittent abnormal slowing and acceleration of the pulse. Hemiplegia and paraplegia he found mostly when the aneurysms had ruptured.

Von Hofmann,[10] in reviewing ten basilar aneurysms which came to his attention during twenty years' activity as chief of the obduction department in Vienna, where postmortem is practiced on every patient dying a sudden death, gives the following symptoms: one patient had no symptoms, another had only headaches, still another had headaches combined with pain in the neck, one had very slight symptoms, one had muscular cramps, one had slight diarrhea and gastric pains a few days before death, one had hemiplegia four weeks before death and in three patients there was no history available.

In the series collected by Rhein,[11] three patients did not present any symptoms; in four the only symptoms

9. Hey: Inaugurations-Dissertazion "Berlin", 1898.
10. Von Hofmann: Wien. klin. Wchnschr., 1894, vii, 823, 846, 867, 886.
11. Rhein: Aneurysm of the Vessels of the Brain, Jour. of Nerv. and Ment. Dis., New York, 1914, xii, p. 360.

were headaches; in nine headaches and some subjective symptoms occurred; in two there was facial nerve paralysis; in one atrophy of the optic nerve; in another paralysis of the oculomotor and abducens nerve, due to hemorrhage; in eighteen death was due to rupture of the aneurysm; in six paralysis of long duration was present, and in six paralysis followed seizure which ended shortly in death; deafness was present in nine patients.

In other cases periodically reported by various authors we find most of the symptoms above cited.

No symptoms: (Apert,[12] Biach,[13] Mathew and Pirie,[14] Reynier,[15] Schmidt[16]) headaches; (Biggs[17]) hemiplegia; (Watson,[18] Schmidt[19]) paraplegia and aphonia; (Ollivier[20]) pain in the forehead, giddiness, restlessness and photophobia, epileptiform attacks two months before death, and mental dulness five days before death; (Amidon[21]) sudden extremely severe headache, unilateral compression of second, fifth, seventh, ninth, tenth, eleventh and twelfth nerves, epileptiform attacks, melancholia, dysphagia and general paralysis; (Klippel et Boeteau[22]).

According to Beadles,[23] the symptoms are those of pressure on the motor tract or the root of the cranial nerves, if the tumor is large; but usually an aneurysm ruptures while its walls are delicate and before it has attained the size of a marble and its flexible and soft wall does not produce much pressure because the arachnoid is abundant in places where they occur; he further states that aneurysms which give rise to cerebral and nerve symptoms are mostly the slow growing,

12. Apert: Ibid.
13. Biach: Aneurysma der Arteria Basilaris, Wien. Med. Wchnschr., 1881, xxxi, p. 1421.
14. Mathew and Pirie: Ruptured Basilar Aneurysm, Neur. and Psychiat. Rev., Edinburg., 1811, ix, p. 107.
15. Reynier: Bull. de la société anatomique de Paris, 1880, lx, p. 167.
16. Schmidt: Berl. klin. Wchnschr., 1880, xvii, p. 293.
17. Biggs: Proceedings of the New York Pathological Society, 1889, p. 107.
18. Watson: An Aneurysm of the Basilar and Middle Cerebral Artery, London, Lancet, 1888.
19. Schmidt: Ibid.
20. Ollivier: Traité des maladies de la moelle épinière, 3ème édition, tome 1., Paris, 1837.
21. Amidon: New York Med. Jour., 1880, xxxi, p. 193.
22. Klippel et Boeteau: Bulletin de la société anatomique de Paris, 1892, lxvii, p. 81.
23. Beadles: Ibid.

thick walled sacs of considerable dimension, which go on for many years and do not rupture, death being in such cases brought about through injury to the cerebral tissue, that is, softening, disintegration, etc., or from some intercurrent malady. Such an aneurysm may cause death through pressure or death may follow apoplexy from rupture of an artery elsewhere. In many cases where postmortem revealed a true aneurysm there have been no symptoms whatever during the life of the patient, except immediately or a very short time before death occurred.

The prognosis according to most authors is bad; it depends on the rapidity of growth of the aneurysm and at what early stage the diagnosis has been made. Some cases have been reported where the lesion lasted for eighteen years, some others where death occurred after seven months; but, of course, there may have been a latent period preceding the attack (Lebert).

Rupture may occur at any time or particles may become detached from the thrombus and death be caused by emboli. The rupture may be brought about by any factor which suddenly increases the blood pressure; that is, by severe coughing or sneezing as in one case described by Schreiner,[24] where all the symptoms of ruptured aneurysm followed an attack of sneezing. The diagnosis made in that case was hemorrhage in the base of the brain and postmortem revealed an aneurysm of the basilar artery.

In almost all cases seen by von Hofmann,[25] death occurred by intermeningeal hemorrhage.

The cause of basilar aneurysm is not clear and is probably governed by conditions which cause aneurysm elsewhere. Trauma may be a great factor mostly overlooked by the patient as the symptoms arise only late, when the aneurysm has reached a large size. (Lebert,[26] Griesinger,[27] Bernheim,[28] Schreiner[29] and Tanton.[30])

24. Schreiner: Inaugurations-Dissertazion, München, 1913.
25. Von Hofmann: Ibid.
26. Lebert: Ibid.
27. Griesinger: Ibid.
28. Bernheim: Die Lehre von den Hirngeschwülsten in Forensischer Beziehung, Friedreichs Blätter für gerichtliche Medizin, 1890, p. 355.
29. Schreiner: Ibid.
30. Tanton: Quelques observations d'anévrismes traumatiques, Bulletin et Mémoirs de la société Chirurgicale de Paris, 1915, N. S. xli, p. 21-24.

Histologic changes in the vessel wall due to irritation, are believed by Lebert to be a contributive factor. The elastic and contractile element is less developed in the cerebral arteries as compared to arteries of similar size elsewhere, and therefore they are more readily influenced.

The laying free of the basilar artery is advanced as a very plausible cause of aneurysm; the walls being not supported by surrounding muscular tissue are more apt to be influenced by any modification of the blood flow; then the sum of the two canals of the vertebral arteries is greater than the lumen of the basilaris and consequently the pressure is greater in the latter (Hey). Further it has been found that the left vertebral artery is frequently of a greater caliber, often taking its origin directly from the arch of the aorta and the irregular force of the blood flow may also predispose to aneurysm (Griesinger,[31] Hey,[32] Lebert,[33] Apert,[34] Lorber[35]). The two latter authors state that this inequality has been found in most basilar aneurysms and that aneurysm is generally found at the site of the most voluminous vessel.

Finally there have been found little rugae in the intima of the basilaris (Balkenartige Vorsprünge; Lebert) which may readily predispose to the formation of thrombi. Davy[36] found such structures in seventeen out of ninety-eight postmortems.

Hyaline and fatty degeneration of the vessel's wall due to various influences is considered by many authors to be the most prevalent cause (Slaviik,[37] Reynier,[38] Roth,[39] Rose and Carless,[40] Reinhardt[41]).

Passed infectious diseases with consecutive endo-

31. Griesinger: Ibid.
32. Hey: Ibid.
33. Lebert: Ibid.
34. Apert: Ibid.
35. Lorber: Thèse inaugurale, Strasburg, 1866.
36. Davy: On a Peculiarity of Structure in the Basilar Artery, Edinb. Med. and Surg. Jour., li, 1839.
37. Slaviik: Etiologie Náhlého úmrti, Prague, 1912.
38. Reynier: Ibid.
39. Roth: Ueber Gehirnapoplexie; Korrespbl. f. Schweizer Aerzte, 1874, N. 6, p. 145.
40. Rose and Carless: Manual of Surgery, 1914, p. 308.
41. Reinhardt: Ueber Hirnarterienaneurysmen und ihre Folgen, Mitt. a. d. Grenzgeb. d. Med. u. Chir., Jena, 1913, xxvi, p. 432.

carditis and emboli are said by Ponfick[42] to be a frequent factor, who described already in 1873 occlusion of the brain arteries by emboli, due to varrucous endocarditis. Endocarditis was also found by von Jacksch[43] in both his cases, with absence of lues and also by Bradford,[44] Eppinger,[45] Hey,[46] and others. Further, mental irritation and overexertion, chronic alcoholism, saturnism, and chronic nephritis is also advanced to be a frequent cause.

Diffuse arteriosclerosis has been observed in quite a few cases in Hey's series and is also prominently mentioned by Eulenburg.[47]

Congenital defects are said by Wichern,[48] Slaviik[49] and Reinhardt[50] to be the most common factor. Status lymphaticus has also been mentioned as a possible etiologic factor in the young (von Jacksch,[51] Schmidt,[52] Loewy[53]).

Considering the sex as a predisposing factor, it is difficult to form an opinion; some authors found a prevalence among men (Apert,[54] Hey,[55] Gouguenheim,[56] Lorber,[57] Oppe,[58] Griesinger[59]). Some authors among women (Wichern,[60] Hofmann[61]).

As to the age, basilar aneurysm seems to be more frequent between 40 and 60 years, but also here it is difficult to give an exact average because in many patients the sex and age was not recorded. A few

42. Ponfick: Ueber Embolische Aneurysmen, Virchow's Arch., lviii, 1873.
43. Von Jaksch: Gehirnaneurysmen, Prager med. Wchnschr., xxxviii p. 483.
44. Bradford: A Clinical Lecture on Certain Aneurysms of the Cerebral Vessels, Lancet, London, 1908, ii, p. 703.
45. Eppinger:
46. Hey: Ibid.
47. Eulenburg: Realenzyclopaedie der Gesammten Heilkunde.
48. Wichern: Klinische Beiträge zur Kenntnis der Gehirnaneurysmen, Deutsch. Ztschr. f. Nervenheilk., Leipzig, 1912, xliv, pp. 220-263.
49. Slaviik: Ibid.
50. Reinhardt: Ibid.
51. Von Jaksch: Ibid.
52. Schmidt: Ibid.
53. Loewy: Zentralbl. f. inn. Med., Leipzig, 1915, xxxvi, p. 469.
54. Apert: Ibid.
55. Hey: Ibid.
56. Gouguenheim: Des tumeurs anévrismales du cerveau, Thèse de Paris, 1866.
57. Lorber: Ibid.
58. Oppe: München, 1892.
59. Griesinger: Ibid.
60. Wichern: Ibid.
61. Hofmann: Ibid.

cases have been mentioned that occurred in young adults and in children.

Heredity may also play a rôle as in the cases described by Klippel and Boeteau,[62] and Watson,[63] where a strong history of insanity was noted.

The diagnosis is extremely difficult because of the variability of the symptoms and especially because of lack of symptoms whatever in a great number of cases; all aneurysms according to Bernheim,[64] may be classified as tumors as far as the symptoms are concerned; this author says: "All localized, circumscribed new formations with tendency to grow inside the cranium produce symptoms due to extension of volume consisting in pressure and brain irritation, general symptoms and finally death." He considers that the important thing for the physician is to bear in mind that there is such a thing as an aneurysm because most of the time it is altogether overlooked.

As for the ruptured aneurysm, the symptoms seem to be more definite and the diagnosis made, according to Langbein,[56] from 1° sudden onset, 2° general cerebral symptoms, 3° bloody cerebrospinal fluid. This author reported one case where all the symptoms were found and on which he based his diagnosis; however, no postmortem examination was made to verify the diagnosis.

The course of basilar aneurysm is variable like the symptoms. The disease may last for many years without giving any discomfort or the symptoms may be extremely severe during all the time and again the aneurysm may rupture and death follow after a few hours. Further, in some rare cases spontaneous recovery has been observed.

Rupture seems to be very frequent and most authors agree that they are followed by sudden death. The following table illustrates the frequency:

62. Klippel et Goeteau: Ibid.
63. Watson: Ibid.
64. Bernheim: Ibid.
65. Langbein: Kasuitischer Beitrag zur Diagnose Perforierender Aneurysmen der Gehirnarterien, München. med. Wchnschr., 1913, ix, 22.

	Total of Basilar Aneurysms	Ruptured Aneurysms
Hey	80	27
Rhein	24	18
Hofmann	10	6
Apert	1	1
Biach	1	1
Bradford	1	1
Wright	1	1
Amidon	1	1
Schreiner	1	1
Klippel and Boeteau	1	1
Total	121	58

The development of the aneurysm is described by Roth[66] as follows: "Prior to the formation of the circumscribed aneurysm there is a diffuse cylindrical dilatation and hypertrophy of the vessel wall followed by atrophy of the media; that is, an amyloid degeneration of the circular muscle fibers. The endoperiarteritis following is a compensatory hypertrophy to make up for the loss of the media; and this has also been confirmed by Zenker, Charcot and Bouchard." He has observed this development in some of his cases but agrees that the process may be variable. According to Hey, the atrophy of the media seems to be the punctum saliens of the whole process and the pathology is the same as in aneurysm elsewhere except that in the basilar aneurysm the laminations are irregular.

The treatment is symptomatologic and palliative only, hygiene, bodily and physical rest, abstinence from overexertion and heat, moderation in eating and drinking, and to keep bowels regularly open. All surgical treatment is considered impossible by Wichern, who says that there is a disturbance of the circulation in the brain due to lack of oxygen, and even if an exact diagnosis has been made surgical intervention is difficult and the few cases where the arteria carotis interna was ligated, have yielded rather unfortunate results.

Oct. 9, 1916.

66. Roth: Ibid.

THE BACTERIOLOGY OF PEMPHIGUS NEONATORUM

FREDERICK HOWARD FALLS

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There have occurred in Chicago eight small epidemics of pemphigus neonatorum within the last year. The disease is an epidemic staphylococcic vesicular dermatitis occurring usually in new-born babies from the fourth to the fourteenth day but capable of being transmitted to older children and adults. The exciting organism is a peculiar strain of staphylococcus which is biologicaly and tinctorially indistinguishable from other strains of staphylococcus, but which shows characteristic pathogenic tendencies when causing the specific disease on the human skin. Morphologically on some media (broth and milk) it differs from the ordinary staphylococcus in that it appears as a kidney-shaped diplococcus with a tendency to form short chains. The writer has cultivated this organism in pure culture from the lesions and it has fulfilled all of Koch's laws with respect to the disease. It is pathogenic for the lower animals killing guinea-pigs and rabbits on intraperitoneal, subcutaneous and intravenous injections in less than a week. However, the typical vesicular eruption could not be reproduced in these animals. An abortive lesion was produced in a monkey. A typical lesion was produced on the arm of the writer from a broth culture of the organism and the latter was recovered from the experimental lesion in pure culture.

The onset of the disease is usually from the fourth to tenth day. A reddened area of hyperemia first appears which becomes whitened in the center in a few hours, followed by a raising of the epidermis into a thin walled wrinkled vesicle containing a clear yellowish fluid. Later this fluid becomes turbid. Smears from the same show pus cells with intra- and extracellular diplococci which in these preparations resemble gonococci very closely but differ in that they are gram positive. The vesicles spread rapidily by peripheral

extension and in severe cases may coalesce to form large areas from which the superficial epidermis has been lifted off, leaving a raw weeping hyperemic base.

There is, as a rule, no rise in temperature or increase in pulse rate. The babies eat and sleep well and gain in weight and there seems to be very little if any subjective sensations produced by the lesions. Fatal cases, however, occur associated with all the signs of a severe septicemia. In most of the reported cases of this type skin lesions were present in the region of the umbilicus. The infection in these cases, therefore, probably spreads by way of the umbilical vessels.

The disease is highly contagious and can be transmitted through the medium of a third party, who is not infected, but who has come in contact with cases of the disease. No cases have been reported in babies that have not been exposed directly or indirectly to the cases developing in the hospital epidemics.

Prompt isolation of cases with quarantine of the obstetrical wards until the last case has left the hospital, followed by thorough fumigation and painting or calcimining the infected wards and sterilizing material that has been exposed to the disease, appears to be the only efficient means of stamping out the infection. While in the hospitals cases should have special nurses and separate equipment for their care. An efficient method of treating the lesions is to rupture the vesicle as soon as it forms and to apply 2 per cent. white precipitate ointment to the lesion. Prophylactic and curative vaccines in doses of 15 millions are being tried, but their use is too limited as yet to permit one to draw conclusions as to their value in preventing or effecting a cure of the disease.

The epidemics have occurred at the West Side Hospital, the University Hospital, Cook County Hospital, St. Luke's Hospital, Michael Reese Hospital, Chicago Lying-In Hospital, Englewood Hospital, and the St. Margaret's Home. Nearly a hundred cases have been observed with at least four deaths.

Further details of the bacteriology of the disease are now in press and will appear shortly in the *Journal of Infectious Diseases*. Further studies are also being made on the epidemiology of the disease.

Nov. 13, 1916.

CYSTADENOMA OF THE PANCREAS

EMIL RIES

This tumor of the pancreas was removed successfully from a woman 56 years old. The patient made a perfect recovery from the operation.

The tumor is the size of a goose egg and oval in shape. It is whitish in appearance and has a sharply defined capsule of connective tissue. At one point there is a piece of normal appearing pancreatic tissue attached to the tumor. On longitudinal section, the tumor presents a picture very much like an orange on cross section. In the middle there is, like a hub of a wheel, a whitish mass of tissue, from which numerous white bands radiate like the spokes of a wheel. These bands interlace and form spaces of irregular shape which appear filled with a homogeneous substance.

On microscopic examination the meshwork of white bands consists of connective tissue which in many places show hyaline degeneration and which carries the blood vessels which are not very numerous. The meshes are lined with a low cuboidal or flat epithelium with small round nuclei and clear protoplasm. These cells are in one layer. The shape of the spaces is very irregular, never quite round, but mostly elongated or quite irregular. The spaces are filled with a granular substance which does not stain either with the eosin or the hematoxylin. The adjoining pancreas show nothing pathological.

The literature contains only two other cases of cystadenoma removed successfully by operation and the case was, therefore, considered worthy of description.

Nov. 13, 1916.

A PRIMARY MALIGNANT NEOPLASM OF THE FALLOPIAN TUBE PROBABLY DECIDUOMATOUS

CLARA JACOBSON

Primary malignant neoplasms of the fallopian tubes are seen sufficiently infrequently to warrant the report of another case. There are recorded in the literature, references to some 150 cases of primary carcinoma, some of these being of disputed diagnosis, about fifteen chorioepitheliomas, and four or five sarcomas. The following case has proved still more interesting because of the difficulty to positively identify it histologically.

The patient, a woman, 20 years old and single, entered Cook County Hospital, March 28, 1915, complaining of abdominal pain and presenting findings and history indicating the diagnosis of an infected ectopic pregnancy. An operation was performed by Dr. R. T. Vaughan and disclosed a large friable bloody mass to the right and back of the uterus. The condition was interpreted as an ectopic pregnancy in the right tube with an old rupture (probably 2 weeks old) into the broad ligament, dissecting apart the layers of the peritoneum. Following a week of continued temperature of 102 to 104 degrees, pulse 108 to 132 and leukocytosis of 20,000, a fluctuating mass was noted in the posterior cul de sac and diagnosed as a pelvic abscess. A posterior colpotomy was performed and about one quart of foul, bloody, purulent material removed and a drain inserted. The patient continued a septic course, feet became swollen and about a week before she died, fresh blood was discharged through the posterior colpotomy wound together with masses of tissue grossly resembling placental tissue. Also, considerable necrotic tissue with a very offensive odor was passed. Hemorrhages and offensive discharges continued until death, May 1, 1915. The essential findings at necropsy were briefly as follows: Fibrous and fibrinous adhesions were scattered throughout the peritoneal cavity. Among adhesions about the laparotomy wound were necrotic pink masses with softened centers. Above the umbilicus were two pink vascular masses 2 to 3 cm. in diameter, adherent to the intestine, and there were a few similar smaller masses among adhesions between the intestines. The pelvis was filled with a mass of necrotic tissue,

pus and fecal material. About this was a wall of purulent necrotic material apparently derived from the pelvic connective tissues. There was a small communication between the sigmoid lumen and vagina through the pelvic abscess. The bladder and uterus were adherent. The ovaries were not found because of adhesions and necrosis. The left fallopian tube was hyperemic and edematous and contained a nodule of soft tissue. The uterus was pressed forward and held by adhesions, but otherwise normal and appeared to contain no decidua. There was thrombosis of the iliac and renal veins. There were no metastases in lymph glands or remote organs.

On microscopical examination, these masses of tumor tissue are found to be of peculiar structure, the characteristic feature being the variety of cells present and the absence of definite arrangement, papillary or alveolar. The cells range in size from 15 to 30 microns, are epithelioid in type, and have large round and oval nuclei 10 to 20 microns in diameter, showing many mitotic figures. Some of the larger nuclei seem grouped together without demonstrable cell boundaries separating them. The larger cells, especially, are highly phagocytic, containing red blood corpuscles, leukocytes and blue staining bodies. There are also a few eosin staining bodies scattered between the tumor cells, and in other places, there are large spaces containing blood, with and without endothelial cell membranes separating them from the tumor cells. Connective tissue as brought out by the Van Giesen stain, is present in comparatively small amount, and this mostly as a capsule. In a section from the fallopian tube from the left side, there is invasion from without, by a cell mass resembling histologically the other tumor masses. This is also well encapsulated. There is present also, edema of the stroma, occlusion of the lumen, erosion of the mucosa and round cell infiltration of the mucosa. Regional lymph glands and other organs are free from metastases. In the uterus we find edema, slight necrosis of the outer portion of the wall but no tumor growths, and no decidua formation. The wall of the pelvic abscess contains comparatively few leukocytes but many tumor cells.

Grossly, the isolated tumor nodules did not suggest deciduoma, being encapsulated and pale, and not of the soft ragged intensely hemorrhagic nature, generally characterizing this form of neoplasm. The pelvic growth was so much altered by infection, that its character had little significance. Microscopically the tumor resembles an atypical chorioepithelioma, the large epithelioid cells being syncytial cells in some places

united to form small syncytial masses, and no typical Langhans cells being found. The histologic findings alone are not sufficiently conclusive to prove positively that the tumor is a deciduoma, but taking the case as a whole, history, symptoms, and physical and autopsy findings, we believe that in all probability the neoplasm arose in the decidua of an ectopic gestation.

Nov. 13, 1916.

(A complete report will be published in Surgery, Gynecology and Obstetrics.)

THE BACTERIOLOGY OF ACUTE EPIDEMIC POLIOMYELITIS *

GEORGE MATHERS

(From the Memorial Institute for Infectious Diseases, Chicago)

The studies of the pathologic anatomy and epidemiology of acute poliomyelitis of Wickman,[1] Harbitz and Scheel,[2] and others, clearly indicated that the disease was infectious in nature, and the earlier work on its etiology was confined to the bacteriology of the infected tissues. These investigations yielded varying results. Early observers found micrococci of different types in poliomyelitis, but the experimental evidence brought forth as indicative of their etiologic importance is inconclusive. The first noteworthy advance towards proving the infectious nature of the disease was announced by Landsteiner and Popper[3] in 1909. They reported experiments in which they had transmitted the disease to two monkeys by the intraperitoneal injection of a saline emulsion of the spinal cord of a child that had died during the acute stage of the disease. At about the same time Flexner and Lewis[4] reported that they had transmitted the disease through several inoculation generations of monkeys.

* The complete paper is printed in The Journal of Infectious Disease, Vol. 20, No. 1, January, 1917, pp. 113-129.

1. Die akute Poliomyelitis bzw. Heine-Medinische Krankheit, 1911.
2. Pathologisch-anatomische Untersuchugen über akute Poliomyelitis und verwandte Krankheiten, 1907.
3. Ztschr. f. Immunitäts., 1909, 2, p. 377.
4. Jour. Am. Med. Assn., 1909, 53, pp. 1639, 1913, 2095.

They also had produced the disease by various inoculation routes, and had demonstrated the infectious material in the spinal fluid, blood, nasopharyngeal mucosa, and lymph nodes near the site of inoculation.[5] The results of these observers were confirmed by many investigators, including Knoepfelmacher,[6] Strauss and Huntoon,[7] Leiner and von Wiesner,[8] and others. Furthermore, Flexner and Lewis[9] and Landsteiner and Levaditi[10] found that the infectious agent was filterable through Berkefeld filters and thenceforth the etiologic agent has been spoken of as a filterable virus.

In recent years the virus of poliomyelitis has been cultivated on artificial media by Flexner and Noguchi,[11] using methods similar to those used in the cultivation of Spirochaeta pallida. In this work small pieces and emulsions of the brain and cord of monkeys dead of acute poliomyelitis were placed in tall tubes of ascites fluid containing sterile fresh rabbit kidney and the tubes incubated under anaerobic conditions. An opalescence appeared around the tissue, usually after five days, which increased until sedimentation occurred, about five days later. Examination of smears of the sediment by the Giemsa method of staining revealed the presence of small globoid bodies arranged in pairs, groups, and chains. Similar bodies were found in microscopic preparations of infected tissue and in glycerinated material. Typical lesions and death were produced in monkeys when such cultures were used for inoculation. These results led to the wide acceptance of the view that poliomyelitis is caused by a filterable virus, the bacteria that had previously been described in connection with this disease being regarded as secondary invaders.

During the summer of 1916 a severe epidemic of acute poliomyelitis prevailed in the eastern states, especially in New York, which stimulated wide-spread interest in this disease, and forcibly impressed the fact that our knowledge of its etiology and transmission was

5. Jour. Exper. Med., 1910, 12, p. 227.
6. Med. Klin., 1909, 5, p. 1671.
7. New York Med. Jour., 1910, 91, p. 64.
8. Wein. klin. Wchnschr., 1909, 12, p. 1698.
9. Jour. Am. Med. Assn., 1909, 53, p. 2095.
10. Compt. rend. Soc. de biol., 1909, 67, p. 592.
11. Jour. Exper. Med., 1913, 18, p. 461.

still incomplete. In Chicago a considerable number of cases occurred, from which the material for this study was obtained. In the light of accepted facts the most important problems in the etiology and transmission of acute poliomyelitis seemed to center in simplification of the methods of cultivation and identification of the infectious agent. Since it had been proved that the virus of this disease is present in the tissues of the central nervous system, fresh postmortem material was used for study; however, the blood and spinal fluid during life were studied bacteriologically in several instances.

In this bacteriologic examination of fresh material from ten cases of acute poliomyelitis a peculiar polymorphic streptococcus-like organism has been isolated in nine instances, in seven of which the growth has been pure. Similar organisms have been demonstrated microscopically in the tissues of the central nervous system of these cases. Cultures of this coccus injected into rabbits, have produced paralysis of various groups of muscles, and characteristic lesions in the central nervous system consisting of hyperemia and edema of the tissues, with hemorrhages, round-cell perivascular infiltration, and neurophagocytosis in the spinal cord, especially in the gray substance, similar to the changes considered characteristic of acute poliomyelitis in man. This micrococcus has been recovered from the lesions in the inoculated rabbits by both cultural and microscopic methods.

The artificial cultivation of the poliomyelitis coccus in an ascites-fluid tissue medium under anaerobic conditions causes changes in the media which cannot be differentiated from those previously described for cultures of the so-called virus of poliomyelitis. Morphologically, also, this bacterium when grown on the same media is similar to the virus, and in stained smears it appears in minute gram-positive coccus-like bodies arranged in pairs, groups, and chains. These minute forms disappear when the organism is cultivated in other media under aerobic conditions.

The morphologic, cultural, and pathogenic characters of the poliomyelitis coccus thus far determined indicate that it is an important factor in the disease.

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CALCULI OF THE SEMINAL VESICLES

T. E. BEYER

Though comparatively very rare, vesicular calculi have not escaped the notice of early observers. Kocher,[1] in his review of the early literature, cites at least a dozen references, including the names of Morgagni and his contemporaries. Collard[2] described their chemical composition and cited Meckel, Vanderviel, Valentin and Hartman as having described them. Beckman[3] reported a single observation; Rokitansky,[4] however, only mentions them. It remained for Reliquet[5] to give us the first clinical history.

More recently Kocher,[6] Rothschild,[7] and Voelker[8] have discussed at some length the clinical history, diagnosis and therapy of spermatic calculi, while Fiolle[9] described the operation for their removal. Still more recently a case has been reported by James and Shuman,[10] in which colic produced by vesicular calculi stimulated nephrolithiasis and led to operation for kidney stone.

Present views are that the formation of spermatic

1. Kocher: Deutsche Chirurgie, 1887, (1), lxvi.
2. Collard: Bull. Soc. Anatom. de Paris, 1826, (2), 255.
3. Beckman, Virchow's Archiv, 1858, (15), 540.
4. Rokitansky: Pathologische Anatomie, 1861, (3), 401.
5. Reliquet: Gaz. de Hôp. Paris, 1879, (52), 891, 915.
6. Kocher: Deutsche Chirurgie, 1887, (1), 632.
7. Rothschild: Lehrbuch der Urologie, 1911, 350.
8. Voelker: Chirurgie der Samenblasen, 1912, (2), 193.
9. Fiolle, La Chirurgie des Vesicules Seminales (Monographies Cliniques sur les Questiones Nouvelles en Med., en Chir., en Biol., 1912, (67), 5.
10. James and Shuman: Surg., Gynecol. and Obst., 1913 (16), 302.

calculi is dependent on the same factors that produce calculi in other organs of the body. The content of the seminal vesicles, normal or inflamed, when evacuation is obstructed is liable to become inspissated and calcareous and in this way calculi and concretions result. They occur usually in elderly individuals in whom there has been a cessation of the sexual function. That there may be a gouty or calcareous disposition is supported by the fact that occasionally other stones have been found in the same body.

The chemical composition of vesicular calculi was first described by Collard, who showed them to consist of the hydrochlorates and sulphates of potassium and calcium as well as a small percentage of albumen and mucus. Obviously not all stones have the same composition, for other investigators mention acid phosphates and the oxids of calcium as the principal constituents. Spermatozoa have been repeatedly demonstrated in the nucleus.

The formation of fistulae from the seminal vesicles is exceedingly rare. They are mentioned in the older literature but none of the cases have been proved post mortem. Guelliot, cited by Voelker,[11] described a case in which spermatic fluid was demonstrable in the rectum but since this occurred only during ejaculation one may conclude that the fistula was probably not direct but rather from the prostate. In another case described by the same author spermatic fluid appeared at fistulous openings in the perineum and on the medial surface of the thigh but since this occurred only during ejaculation one must again conclude that the fistulas passed through the prostate.

The clinical symptoms produced by vesicular calculi have first been described by Reliquet,[12] and little has been added to his excellent account. Pain in the perineum, priapism, painful coition with failure to ejaculate, painful and frequent urination are the important symptoms. The pain in the perineum is very sharp and colicky in character, centralized about an inch up the rectum or at the neck of the bladder. Sometimes

11. Voelker: Chirurgie der Samenblasen, 1912, (2) 56.
12. Reliquet: Gaz. de Hôp. Paris, 1879, (52) 891, 915.

it radiates up the posterior wall of the pelvis or to the testicles giving rise to the so-called spermatic colic which has been confused with colic produced by kidney stone.

The following case is reported because among other interesting conditions there were a large number of calculi in the seminal vesicles.

C. S., a Jew, 63 years of age, was brought to the Cook County Hospital in moribund condition by the police and entered to the service of Dr. Thompson. No history was obtained except that he had been injured two months previously. Death occurred on the third day after entrance and meningitis following skull fracture was found as the cause of death. In the urogenital organs the following conditions were found:

"The right testicle is absent. On the right side of the scrotum there is an old gaping wound, 3 cm. long, from which yellowish white pus escapes. One cm. to the right of the upper attachment of the scrotum there is a recent scar, 1.5 cm. long and 5 mm. wide, covered with dried blood. At the root of the penis there is a scar 3 cm. long and 1 cm. wide. Here there are also small pockets of pus and a fistulous passage. On the under surface of the penis 2 cm. proximal to the glans there are ten to fifteen small abscesses covered with dried blood. There is no urethral discharge.

"On opening the urethra a large amount of pus escapes. The bladder is small and contracted, its walls markedly thickened. The mucosa is in folds, many of its vessels engorged and dilated, and it is covered by a layer of thick, greenish foul-smelling pus.

"The seminal vesicles are large and distended, the capsules covering them tough and thickened. On palpation there is crepitus from the presence of numerous contained calculi. The ducti deferentia are apparently normal and their ampullae contain no calculi. There are no fistulae from the seminal vesicles or spermatic ducts.

"The prostate is normal in size and consistency. The prostatic urethra, however, contains four fistulous openings which contain calculi of varying sizes. On removal of a large number of these there are disclosed four distinct, tortuous, noncommunicating fistulae, passing more or less directly through the prostate and connecting the prostatic urethra with the seminal vesicles. Through these new and adventitious passages the seminal vesicles are emptied of their stones.

"Two of the fistulous openings in the prostatic urethra are situated in the usual location of the prostatic ducts, a third displaces both mouths of the ejaculatory ducts. These openings are oval and 8 mm. in greatest diameter. The fourth, 2 mm. in diameter, is on the left side 1 cm. proximal to the one displacing the mouths of the ejaculatory ducts. All are valve-like and resemble a patent foramen ovale.

"All told 157 stones are removed, fully two thirds from the right side. They vary in size from a millet seed to a pea. The larger white ones are soft and quite readily crushed with the fingers, the smaller are hard and facetted. All are covered with gray viscid muco pus which sticks them loosely together."

In the absence of any clinical history it is practically impossible to trace the exact sequence of events which resulted in these marked changes. It is probable that the calculi resulted from primary changes in the seminal vesicles and that the fistulae resulting allowed the escape of stones into the urethra where by irritation and infection an organic stricture resulted. On the other hand, the urethral stricture may have been primary and may have by obliteration of the prostatic and ejaculatory ducts contributed indirectly to the formation of calculi in the vesicles. Whatever the primary condition, it is certain that the changes at the base of the penis and in the scrotum are the direct outcome of urethral stricture complicated by infection and the presence of stones. Whether any of the calculi found their way into the scrotum or perineum seems not only possible but quite probable.

An attempt to drain the scrotal abscess resulting from the extended urethral infection explains the old gaping wound on the right side of the scrotum. This evidently failed in its object and castration had to be resorted to; hence, the recent scar at the upper attachment of the scrotum can be accounted for. The scar at the base of the penis is such as usually results from external urethrotomy.

Dec. 11, 1916.

PRIMARY NONPIGMENTED SARCOMA OF THE SKIN

E. P. ZEISLER

Of the infrequent solitary, nonpigmented variety of cutaneous sarcoma, two cases observed by the author were reported.

Case 1.—Primary, nonpigmented, spindle and giant-celled sarcoma of the skin (sarcoma giganto et fusocellulare). Cartilaginous yellow nodule, 1 cm. in diameter, situated deeply on the chin of a 19 year old girl. Regional glands not involved. Duration ten months. Recurred once after previous excision. Complete excision followed by radium therapy resulted in cure without recurrence to date. Microscopic examination showed a spindle and giant-celled sarcoma involving the corium and subcutaneous tissues. In the deeper strata of the tumor were numerous large giant cells resembling more the Langhans or foreign-body type than the true myeloplax type.

Case 2.—Primary, nonpigmented spindle-celled sarcoma of the skin developing after trauma. Bluish-red nodule on the arm with hard border and ulcerated center developed 2 months after a burn by a belt. Regional glands not involved. Surgical removal was followed by cure without recurrence to date. Histological examination showed infiltrating sarcoma of the pure spindle or oat-celled type undergoing ulceration in the center.

Dec. 11, 1916.

DEFORMITIES OF THE EAR

J. HOLINGER

The pyramid of the deformed temporal bone of a new-born was decalcified, cut and stained. Owing to the poor state of preservation no important conclusions could be drawn. The microscopic details of the membranous labyrinth were mostly lost, though the different cavities, the vestibulum, the semicircular canals were clearly recognized. No definite statements about the middle ear and external canal can be made.

The literature abounds in descriptions of deformities of the external ear, but the microscopic examinations are very few. A general review of the whole subject is lacking. The following questions were studied and answers found in embryology:

1. Why have congenital deaf-mutes usually well formed external and middle ears?

2. Why are deformities of the labyrinth leading to deaf-mutism usually in both ears, and deformities of the external ear confined to one ear only?

3. Why are deformities of the middle and external ear so often combined with deformities of the lower jaw, especially absence of the ramus ascendens?

Dec. 11, 1916.

LEUKOPENIA AND LEUKOCYTOSIS IN RABBITS

CLIFFORD W. WELLS

In the blood of normal rabbits the leukocytes varied from 3,300 to 14,650 per cubic millimeter, with an average of about 9,000. Normally, there were fewer per cubic millimeter in the blood of the left ventricle than in that of the right. The blood from the normal liver and lung parenchymata contained approximately the same number of leukocytes as the blood in the general circulation, while in that from the splenic parenchyma the number was several times greater.

Following the intravenous injection of bacteria there regularly occurred within a few minutes, usually less than ten, a great reduction in the number of leukocytes in the general circulation, chiefly involving the polymorphonuclear cells. The decrease, which amounted to 11,000 cells per cubic millimeter in some instances, was not dependent on the quantity of bacteria injected. The lowest count recorded was 1,250 leukocytes per cubic millimeter. The blood from the bone marrow, liver, and splenic parenchyma contained a greatly increased number of leukocytes, especially the blood from the latter, in which the count overreached 180,000 in several instances. The increase of leukocytes in the blood from these sources consisted largely of polymorphonuclear elements. The blood from the lung parenchyma did not contain an increase either in the number or proportion of the polymorphonuclear leukocytes. Late during the leukopenia, blood from veins of the internal organs and from the left ventricle contained more leukocytes than did that from the corresponding arteries and right ventricle. Sections of liver, spleen, and bone marrow revealed a hyperemic condition, especially marked in the case of the spleen.

From four to fifteen hours after intravenous injection of bacteria there occurred a great increase of leukocytes in the blood of the general circulation, con-

sisting largely of polymorphonuclear cells. No direct connection was observed between the quantity of bacteria injected and the height of the hyperleukocytosis. Sections of lung, spleen, and liver showed marked hyperemia; of the bone marrow, hyperemia and increased leukoblastic activity.

Dec. 11, 1916.

VASCULAR LESIONS IN CHRONIC PROTEIN INTOXICATION

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The literature contains but few references to vascular lesions in acute anaphylaxis, and almost no references to vascular lesions produced by repeated injections of foreign proteins. Some investigators have reported fatty changes in capillary endothelium, due to acute anaphylaxis, but those who have studied chronic protein intoxication have not reported vascular lesions. The author, in studying the lesions produced in the kidneys of guinea-pigs by repeated injections of foreign proteids, noted distinct lesions of a degenerative type in the smaller arteries. The present report concerns a continuation of this work, with special reference to vascular lesions occurring in various organs. Guinea-pigs only were used, and the attempt was made to give each animal as many anaphylactic shocks as possible during the experiment, using egg-white and beef serum.

Arterial lesions were observed in all organs studied, except lungs, but were most frequent and most marked in the liver. The lesion apparently begins with edema of the endothelium. This is soon followed by a granular degeneration and vacuolation of the cells, sometimes accompanied by fissuring of the intima. The nuclei may disappear, and sometimes may have the appearance of having been cast off. Soon the stage of regeneration occurs, the nuclei of

the endothelial cells being much increased in number, and appear round instead of oval when the artery is viewed in cross section. Edema is noted about the internal elastic lamina, so that the lamina may be rendered quite prominent, and it is frequently swollen and occasionally split or frayed. Frequently the swelling and fissuring extend also to the media. No distinct proliferation of connective tissue was noted.

The most severe lesions were found in animals dying in shock, or killed within one week from the time of the last injection. In animals killed five weeks or longer after the last injection, the lesions were still present, and frequently well marked, but were less severe than in the first group. The lesions were noted in 100 per cent. of livers, 66 per cent. of kidneys, 66 per cent. of hearts, and in 100 per cent. of the five spleens examined.

The aortas in this series were practically without pathological change; the vasa vasorum of the aortas were normal. Perivascular infiltration was found in 60 per cent. of the experimental animals, but was usually not very severe. Lesions of the type here described were found chiefly in the smaller arteries, rarely in the larger arteries, or veins, and not at all in the capillaries, except in the capillaries of the glomerular tuft as previously described.

Jan. 8, 1917.

FOUR RARE TUMORS OF THE VAGINA

EMIL RIES

Tumors of the vagina were demonstrated as follows:

1. Infravaginal cyst lined with stratified epithelium from which solid pegs of epithelium start out into the surrounding tissue: Cyst due to misplaced epithelium in consequence of injury during labor.

2. Infravaginal cyst lined partly with stratified and partly with columnar epithelium, the latter forming glands. Cyst due to remnants of the Wolffian duct.

3. Two solid tumors of polypoid shape from the lower part of the vagina consisting of granulation tissue growing in partly healed lacerations due to labor and observed many months after labor.

4. Two polypoid tumors from one vagina about twelve months after abdominal hysterectomy for adenocarcinoma of the uterus. The tumors are on the surface of the vagina and the underlying tissue is entirely free from tumor and there is no recurrence in the scar of the hysterectomy.

Jan. 8, 1917.

DEMONSTRATION OF METHODS FOR THE DETERMINATION OF HYDROGEN-ION CONCENTRATION

J. H. LONG

Many processes in the animal body are dependent on the hydrogen ion concentration of the medium in which they take place. This is notably true of the digestive reactions. In recent years much attention has been given, first to the development of methods employed in these determinations, and then to special applications such as the accurate determination of the ion concentration of the blood, urine, intestinal juice

and other body fluids in normal or pathological conditnon.

Two general schemes or methods of procedure are in common use. The first is known as the indicator method and depends on the fact that many indicator solutions show a gradual change in color, within certain narrow limits, in passing from one degree of acidity or alkalinity to another. These changes do not usually take place at the true neutral point. With methyl orange, for example, the changes all occur in the acid zone, a rather marked excess of hydrogen ions in solution being necessary to strike the acid color, while with a somewhat lower concentration the color is a transition tint between that of alkalinity and acidity.

By adding a proper indicator to a very weak acid or alkaline solution, and the method is applicable only to weak solutions, a certain color is produced, and this depends on the H or OH concentration. This corresponding concentration is found by adding the same indicator to a series of solutions of known hydrogen ion value until one is found which gives the same shade as the one under examination. This is titration by matching colors and does not involve the use of acid or alkali. Salm, Michaelis, and especially Soerensen have devised standards of definite hydrogen ion strength which may be used for these comparisons.

Experiments were made illustrating these titrations which are limited, of course, to clear or nearly clear and colorless solutions.

The second and more widely applicable method of finding the H-ion concentration is the electrometric and depends on the measurement of an electric potential developed. No one of the body fluids is exactly neutral. It must contain an excess, which may be very slight, of hydrogen or hydroxyl ions. For this reason a particular fluid may be made a part of a peculiar galvanic cell in which the osmotic pressure of the hydrogen ions is opposed by the so-called solution pressure of a hydrogen plate immersed in it. The potential developed by this relation is the factor determined, just as we may measure the potential produced

by a zinc plate immersed in a dilute zinc sulphate solution. In either case the potential is a function of the concentration of the solution.

The method was illustrated by the determination of the very weak acidity of some filtered stomach contents. This was contained in a special kind of cell filled with hydrogen gas. In the liquid a platinum plate covered by platinum sponge was partly immersed, and the platinum so treated became in effect a hydrogen plate because of its absorption of the gas in large amount. This plate was connected on the outside of the cell with a potentiometer. The liquid part of the cell, that is the stomach fluid, was connected by means of a calomel electrode with the other pole of the potentiometer which permitted a determination of the potential by comparison with that of a standard Weston cell, through a modification of the so-called compensation method.

By means of a proper formula, originally developed by Nernst, the potential so found may be translated into terms of the hydrogen-ion concentration responsible for the osmotic pressure of the solution. That is, the determination is possible because of the causal relation between pressure and potential.

Charts were shown giving the hydrogen and hydroxyl concentrations of a number of fluids of physiological importance, with some variations in disease. Applications in various directions were discussed.

January 8, 1917.

A CASE OF GLIOMA OF THE FOURTH VENTRICLE WITH PIAL METASTASES

PETER BASSOE

(From the Presbyterian Hospital, Chicago)

The following case is unusual in two respects: first, because of the rarity of metastases of glioma and, second, because of the repeatedly positive Wassermann test on blood and spinal fluid during a period of two years and the absence of definite syphilitic lesions at necropsy.

A waiter, 37 years old, was referred to the writer by Dr. C. Joseph Swan on Jan. 11, 1915. He gave a history of chancre when in Manila fourteen years previously. It was considered a soft one and no secondaries developed. In the summer of 1914 he gradually developed diplopia with convergent strabismus. He consulted Dr. Swan in October, 1914. Both external recti were weak. A Wassermann test on the blood at the Chicago Laboratory was strongly positive. Mercurial injections and two injections of neosalvarsan were given but the paralysis of the external recti gradually grew more complete. When first examined by the writer he presented no other symptoms. On Jan. 12, 1915, examination of the blood and spinal fluid by Dr. H. K. Nicoll showed strongly positive Wassermann reaction with both blood and spinal fluid. The latter gave negative Nonne-Apelt and Lange gold tests and a cell count of eleven lymphocytes per cubic millimeter. More mercury and neosalvarsan were administered without improvement. No new symptoms developed until March, 1916, when the upper lip began to feel stiff. On May 16, the Wassermann test with the blood was weakly positive, with the spinal fluid fairly strongly positive. Nonne and Lange tests negative, cell count four. When readmitted to the hospital on August 2, he had well marked facial paralysis on the left side, slight on the right side. The internal recti were also weak. On August 4, examination of the spinal fluid showed strongly positive Wassermann test, positive Nonne test, weakly positive Lange test (1112210000) and a cell count of fifty-nine. Swift-Ellis treatments were given on August 4 and 18, but the patient grew worse. The knee and ankle jerks became increased, more so on the right

side and a Babinski sign developed on the right side. The abdominal reflexes were weak. From the middle of July he noticed weakness of the jaws in chewing and developed considerable gastric disturbance, with frequent vomiting. On August 18, Wassermann test with the blood was negative, with the spinal fluid strongly positive. Cell count 16, Nonne positive, Lange test positive (1234410000). Difficulty in swal-

Fig. 1.—Secondary glioma on posterior cervical root. From enlarged photograph.

lowing set in durng the last week of August. For the first time during his entire illness he suffered from headache and pain in the neck. Hiccough set in, followed by weakness of pulse and respiration. He finally became cyanotic and on September 11 the temperature began to rise, reaching 104.4 F., before death on Sept. 12, 1916.

The *clinical diagnosis* was cerebral syphilis and the only question was whether the multiple cranial nerve paralysis was due to involvement of the nerve roots by the syphilitc meningitis or whether the nuclei were affected by ischemia from syphilitic arteritis. The necropsy was held by Dr. B. O. Raulston, resident pathologist of the Presbyterian Hospital, twelve hours after death.

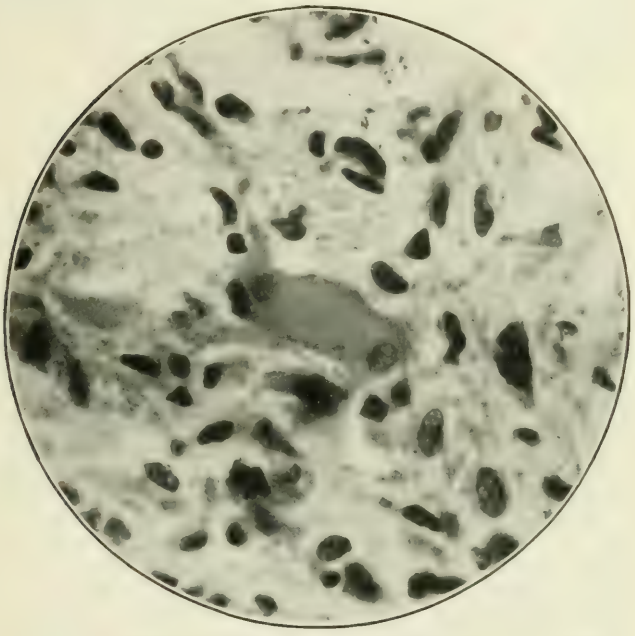

Fig. 2.—Secondary glioma on ventral surface of pons. High power.

Anatomic Diagnosis.—Tumor mass in the medulla oblongata and the cervical portion of the spinal cord. (Gummata?) Syphilitic aortitis. Moderate hypertrophy of the spleen. Healed tuberculosis of the tracheobronchial lymph nodes and of the upper lobes of both lungs. Small abscess in the upper lobe of the right lung. Moderate passive hyperemia of liver, spleen, kidneys and intestines. Few petechial hemorrhages in the lining of the stomach and renal pelves. Small shallow traction diverticulum of the esophagus; redundant sigmoid.

The description of the heart is as follows: "There are no evident gross changes in the heart valves. The heart muscle is brownish red, is of usual firmness and there are no grayish fibrous streaks or sunken portions in it. The lining of the coronary arteries is made uneven by numerous yellowish, small, irregular, elevated plaques. The foramen ovale is closed." No special description of the aorta is found, but it is stated that the intima of the splenic artery is roughened by yellowish plaques and that the hepatic artery shows sclerosis similar to that found in all the other arteries.

The brain and cord were hardened in formaldehyd solution and later further examined by the writer.

The brain weighs 1,420 grams. There is no change in the dura. The pia of the convexity is smooth. At the base there is slight grayish thickening over the ventral surface of the pons anteriorly, at the exit of the third nerve, more so on the right side. At the junction of the pons and bulb there is much more marked grayish thickening, involving the roots of the sixth and seventh nerves on both sides. There are three localized plaques, each rounded and 1 cm. in diameter—one in the median line between the two sixth nerves, lying altogether on the bulb, the other two in the lateral recesses impinging the seventh and eighth nerves. That on the left side is thicker, projecting 1.5 mm. from the surface. A grayish mass is seen to fill the lower portion of the fourth ventricle. It is firmly adherent to the pons and bulb reaching the lower end of the ventricle but separates quite readily from the cerebellum. On splitting the cerebellum, the tumor is seen as a grayish red semiglobular mass extending along, and firmly attached to the whole floor of the ventricle. It measures 3.5 cm. anterioposteriorly, 3.5 cm. transversely and projects 1.5 cm. into the ventricle. There is a small recess at the posterior end of the aqueduct containing the anterior and free end of the tumor.

On cross section the lateral ventricles are only slightly dilated but the third ventricle shows more marked dilatation. The posterior horn on the right side is more than twice as large as the left which is not materially dilated.

On cross section of the bulb through the tumor the latter is found to measure 1.5 cm. anteroposteriorly, the remainder of the pons measuring 2 cm.

The growth in the pons is grayish red with many hemorrhagic areas. It gradually diminishes in thickness and ends at the anterior end of the pons.

The spinal dura shows no change. On slitting it posteriorly an elevated roundish grayish patch is found in the lower cervical region chiefly to the left on the median line (Fig. 1).

Some posterior root filaments are inbedded in it. In the mid thoracic origin slight grayish thickening is seen along the posterior surface for a distance of 4 cm.

Histologic Examination

The Tumor in the Fourth Ventricle is very vascular, rich in thin walled vessels and in places extensive hemorrhages. Areas of necrosis are also seen. The tumor is made up of a loose meshwork of cells and fibers. The former are very

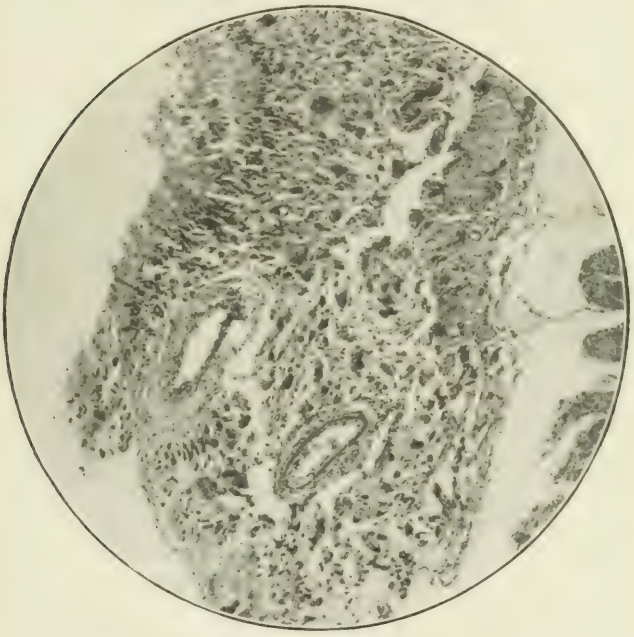

Fig. 3.—Secondary glioma on cervical root. Low power.

variable in size and shape. Most of them are round or oblong, sometimes also spindle shaped with feebly stained usually homogeneous cytoplasm and oblong nuclei deeply stained and usually at the periphery of the cell. Here and there much larger cells are seen, most of them also round or oblong with relatively small nuclei, while others have seven or eight nuclei or contain dozens of small chromatin granules. Some of the large cells are elongated and possessed

of one or more long processes. The cells are often found to radiate about the vessels.

The tumor is seen to be intimately connected with the pons which is infiltrated for a considerable distance and there is no sharp demarcation between the tumor and pons structure. This is best seen in Pal-Weigert specimens which show a broad zone containing an admixture of tumor tissue and medullated fibers.

In specimens stained with Weigert's glia stain and still better by Mallory's phosphotungstic acid — hematoxylin method, a dense network of fine fibers is seen, and with the last named method, the fibers can frequently be traced to cells. In many areas the more or less palisade-like parallel rows of cells suggest origin in ependyma.

The nodules on the ventral surface of the pons show a similar structure but vessels are less conspicuous and there is less necrosis, while a relatively larger number of large cells are seen. Such a cell with processes is seen in Figure 2.

The nodule in the posterior surface of the cervical cord, the gross appearance of which is seen in Figure 1, is found to be connected with the pia over a posterior root, portions of which pass through the nodule. As seen in Figure 3 these nodules show in exquisite manner cell columns imitating ependyma. On the outside of this structure a dense network of fine blue fibers may be seen in phosphotungstic acid hematoxylin specimens and similar fibers are seen throughout the nodule. Numerous large cells similar to those described above are also seen.

Sections from the thoracic, lumbar and other portions of the cervical cord, in many places show small collections of cells, about the pial vessels in the vicinity of the posterior roots. Most of these cells are small with deeply stained round, oblong or triangular nuclei but a few large cells are also seen. Altogether this tissue surrounding the posterior root has the appearance of glia and not that of an inflammatory infiltration.

Pal-Weigert specimens of the cord show a minimal degree of degeneration in the columns of Goll in the cervical region. There is no appreciable degeneration of the posterior or anterior roots nor is there any appreciable degeneration in the pons except in the portions blended with the tumor.

Throughout the specimens from the nervous system the vessels show considerable thickening and in places hyaline degeneration of the intima.

Internal Organs: Sections from the lungs, spleen, liver, pancreas and kidney shows no change of interest.

Jan. 8, 1917.

STUDIES IN GAS GANGRENE

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SUMMARY

An examination of the uniforms of Belgian soldiers for spores of anaerobic bacteria of the group capable of causing gas gangrene showed, (1) that 100 per cent. of the uniforms of men from the trenches carried spores of anaerobic bacteria, and of these 90 per cent. carried spores of organisms belonging to the group of B. welshii; (2) that within three days after sterilization by the method employed in the Belgian Army, about 66 per cent. of the uniforms again became contaminated with spores of these bacteria when the men remained in the barracks instead of returning immediately to the trenches; (3) that the new uniforms as received by the Belgian soldiers and the cloth from which these garments were made, contained spores of this group of organisms in the meshes of the goods in all samples examined.

A series of twenty recent wounds were examined for the presence of organisms capable of causing gas gangrene. The material consisted of fragments of shells or hand grenades, bits of clothing and other débris, and pieces of lacerated tissues and blood clot removed from the wounds immediately after the arrival of the patient at the hospital (Ambulance de l'Océan, La Panne, Belgium). The interval of time between the receipt of the wound and the removal of the material for examination was in most cases from two to eight hours. In this series of twenty cases, 75 per cent. of the fresh wounds contained either spores or vegetative forms of baccilli having the morphology and biological characteristics of the group of B. welchii. Only 20 per cent. of these patients, i. e., 15 per cent. of the whole series, developed gas gangrene. In each instance the wound involved the large muscle masses of the thigh with much laceration of the tissues. The

organisms reached the wounds in the form of spores only. It was only in the deep-lying injured muscle that conditions were favorable for germination of these spores and rapid multiplication of the bacilli, namely, anaerobiosis and a culture medium rich in fermentable carbohydrate (glycogen). In the pathogenesis of this infection in contaminated wounds, therefore, the lacerated muscle is the most important factor, and it is to this that attention should be directed in the prevention of the disease.

Because the presence of a fermentable carbohydrate is essential to the growth of B. welchii, and because cane sugar has been used in the treatment of war wounds, 75 per cent. of which were found to be contaminated with spores of this group of organisms, it seemed desirable to study the effects of different concentrations of saccharose on their growth. All of the ten strains studied multiplied rapidly and produced an abundance of gas in broth containing 5, 10, 20 and 40 per cent., respectively, of saccharose. In the 40 per cent solutions the formation of gas was somewhat slower than in the lower concentrations. Only one strain produced gas, slowly, in 50 per cent. saccharose broth. None of the strains grew or produced gas in bouillon with 60 per cent. of cane sugar.

In the treatment of gas gangrene in the war zone, one of the most effective methods is the injection of pure oxygen gas into the affected and adjacent tissues. In order to investigate the mechanism by which pure oxygen in the tissues produced its apparent salutary effects, the gas was allowed to bubble through tubes of anaerobic milk containing B. welchi, for varying periods of time. It was found (1) that different strains did not always show the same resistance to the presence of oxygen; (2) that, after three hours' incubation, bubbling oxygen gas for twenty minutes through milk cultures did not appear to inhibit the growth in any way for the tubes showed typical stormy fermentation after a further twenty-four hours in the incubator; (3) that bubbling oxygen for twenty minutes through less heavily inoculated tubes of milk caused death of the organisms in from four to twelve hours; (4) that

bubbling the gas through such milk tubes for five to ten minutes did not destroy the bacteria but either inhibited their growth or changed their ability to act on lactose so that there was only coagulation with little or no gas formation.

Feb. 12, 1917.

RECENT STUDIES IN BLOOD SUGAR

HUGH McGUIGAN

If picric acid be used to precipitate the proteins from blood, the excess of the picric acid need not be removed, if the sugar is to be determined by the Fehling-Bertrand, i. e., the permanganate method. In using this method we found the sugar content of normal blood comparatively low — on the average below 0.5 per cent. By using the Benedict colorimeter method the same blood would average at least twice this amount and often more. This would indicate that a part of the sugar is free and a part combined, a conclusion at variance with the work of von Hess and myself (*Jour. of Pharmacology and Therapeutics,* 1914, Vol. 6, p. 45).

This and the very varying results of others on the normal level of the blood sugar caused me to investigate the subject in detail.

In the first place, I thought that a polymerized or combined form of carbohydrate existed in the blood. This was supported by the fact that if the blood filtrate free from proteins be boiled with acid we obtained results approximating closely the result obtained by the Benedict colorimetric method. To do this, however, we had to use a certain amount of acid, which was not neutralized before the use of Fehling's solution. This apparent unethical procedure was adopted because of the very great variation in the alkalinity of Fehling's solution recommended by various authorities, and especially from the fact that in known solutions of dextrose in water solution treated in exactly the same way, no variation in the yield occurred. This,

however, is a grave error, and one that has apparently been overlooked by most workers in the blood sugar field. A standard solution of dextrose in water is not the same as the same amount of sugar in the blood. This is clearly evident by the great variation in the blood sugar yield obtained by the use of different so-called Fehling solutions.

In common use the alkaline part of Fehling solution varies from 50 to 125 gm. of KOH in 500 c.c. Such a variation in alkalinity causes little variations in the yield obtained from a known dextrose solution in water, but it gives enormous differences when used to determine the sugar in the blood.

The present United States Pharmacopeia IX uses 50 gm. KOH in 500 c.c. U. S. P. VIII recommended 75 gm. and VII recommended 125 gm. If blood be glycolyzed aseptically until all the sugar has disappeared, or if a solution of dextrose be fermented with yeast until the sugar has all disappeared, any sugar that is now added to the filtrate can not be completely recovered if we use the strongest alkaline Fehling, while it can be recovered if we use the weaker. The result here is not due to a destruction of the sugar by the strong alkali because if after boiling with this we add sufficient acetic acid to reduce the alkalinity to the weaker concentration we still can obtain the added sugar.

The above facts, I think, explain the great variation in the concentrations of sugar in the normal blood. Some have used weak alkaline Fehling's. Some the strongest reported. All have standardized their solutions in water and this will not hold for blood filtrates, no matter what means are used to clarify. What the interfering body is in blood we have not discovered.

In the present work leading to the above conclusions I precipitated the blood, after laking, in water with saturated picric acid. Ten c.c. of blood was drawn from the jugular vein and measured into about 20 c.c. of water. After ten to fifteen minutes about 0.5 gram solid picric acid was added, the whole stirred well and made to 150 c.c. with saturated picric in water. This mixture was shaken, filtered and 100 c.c.

of the filtrate taken for analysis = 6.66 c.c. blood. The Fehling used was varied in strength because we were studying this question.

If we take the solution used by Morris in his Clinical Laboratory Methods, Appleton & Co., New York, it contains:

I. Copper sulphate ..... 34.65 gm.
Distilled water to 1,000 c.c.
II. Rochelle Salt .....173.0 gm.
Sodium hydrate .....125.0 gm.
Distilled water to 1,000 c.c.

We used 30 c.c. of each of these and then brought the picric filtrate and the Fehling to boiling in separate beakers. Now put the Fehling into the blood filtrate and continue to boil two minutes. Filter through an asbestos in a Gooch crucible. Wash free from picric acid, remove the asbestos and copper precipitate to the beaker in which the copper was reduced, wash crucible and the beakers with about 40 c.c. warm water, and 25 c.c. 5 per cent. ferric sulphate in 20 per cent. sulphuric acid. The amount of iron reduced was measured by titration with potassium permanganate of such strength that 1 c.c. = 0.001 gm. dextrose. Determined in this way the normal blood contains about 0.02 per cent. dextrose or less. If, however, instead of the above Fehling's mixture we use the strength recommended by the Pharmacopeia we will obtain about 0.1 per cent. This is about the figure given by the Benedict colorimeter method.

Résumé: For the determination of sugar in the blood, by Fehling's solution, great variations are found depending on the strength of the alkali used. As found in the literature dealing with blood sugar concentrations, great variations of this alkalinity have been used. The cause of the variation is due either to something in the blood filtrate interfering with the determination and perhaps holding cuprous oxid in solution or preventing its precipitation or it may be due simply to the fact that the more weakly alkaline solution is a more delicate reagent than the stronger. In a water solution the variation under the same conditions is

relatively small and unimportant. The relation of the copper sulphate to the alkali is also important—increasing the copper, acting like a decrease in alkalinity. Variation of the copper is rarely or never encountered in the literature and I have not discussed it here. For blood sugar work the strength of KOH should be 50 gm. to 500 c.c. of the alkaline solution. This is the pharmacopeial strength and is the Soxhlet modification of Fehling's solution. Stronger solutions of alkali give a smaller yield of sugar and if too strong (125 gm. NaOH, or equivalent to 500 c.c.) decidedly too low results are obtained. The variation in alkalinity seems to be the most important factor in accounting for the variation in the normal blood sugar level reported by workers in this field.

Feb. 12, 1917.

TWO ARACHNOID CYSTS

E. R. LeCOUNT AND KAETHE DEWEY
(From the Pathological Laboratory of Rush Medical College)

Cysts strictly bound within the sheets of the leptomeninges are the rarest type of those occurring about the brain. The largest number of them have been discovered by surgeons in exploratory trephining after trauma, and in Jacksonian epilepsy and other symptoms of cerebral involvement. Other cysts are on record which had not given any clinical symptoms whatsoever during life and were only discovered at the post mortem examination. Among these are some of the largest arachnoid cysts which have been so far described. The most remarkable case is one reported by Klebelsberg. This cyst was as large as a fist, discovered at the autopsy in a man 78 years old. There had been no clinical symptoms from it. Most of these latter cysts have been considered as due to anomaly in the development or the results of brain defects, inherited or acquired.

The two cysts described in this report were found at the post mortem examination. One is unusual on account of its size. The depression on the brain measures 7.5 by 7 cm. in

diameter, and fully 2.5 cm. in depth. It occupies the right frontal lobe and takes in the whole inferior frontal convolution, parts of the median frontal gyrus and the lowest part of the anterior central convolution and extends backward into the temporal lobe. The sac of the cyst was formed from the leaflets of the arachnoid; the surface of the brain on the floor of the cyst is covered by an extremely thin membrane which consists of pia and a delicate sheet of arachnoid, which can be recognized as such by the fact that it does not dip down into the fissures with the pia. The delicacy and transparency of the membrane in this region stands out in marked contrast to the opacity and thickening of the pia arachnoid covering the brain outside the depressed area. The thickening is most pronounced in the immediate neighborhood of the cyst. On the base of the brain it is slight. The cisterna magna has evidently been considerably thickened. The vessels show a slight degree of arteriosclerosis. The dura is adherent to the underlying tissues on both sides of the sagittal sinus.

The clinical data are scanty. The patient, a man of 67 years, was brought to the Hospital of the House of Correction in a condition which was diagnosed as delirium tremens. He had had a pint of whiskey that day. He had been an habitual drinker for 40 years, but had never had delirium tremens before. There had been no fall, no convulsions, no unconscious spell. In examining him nothing was found about the head; there was a tremor, a left sided pleurisy, râles all over the chest, with rapid respiration, a fairly full pulse with fairly full tension. The head was retracted and the neck muscles were slightly rigid. The reflexes below the thorax were absent, except the plantar reflex which was quite active. There was no Babinski. There was involuntary movement of the bowel and urinary bladder. Death occurred 7 days after his admission to the hospital. Delirium tremens and a possible tuberculous leptomeningitis was the diagnosis. At the postmortem examination the skull was found unbroken; there were no changes in the middle ear and no hemorrhages in the pericranial tissue. The brain weighed 1,340 gm.

In histologic preparations from the marginal region of the cyst the thickening of the arachnoid outside the depressed area is very marked. The endothelial cells lining the outer surface are proliferated and closely set. The lower sheet of the arachnoid is continued downward from the margin over the pia along the floor of the cyst. The arachnoid nature of this sheet is well demonstrated by the presence of psammomatous structures of various size in practically all sections

from this region. The pia is somewhat distended by spaces surrounded by exceedingly delicate connective tissue fibers. The vessels have thickened walls, many of them in a state of hyaline degeneration. The surface of the brain is irregular and has baylike depressions and indentations, but there is nowhere an adherence of the membrane to the brain. There are no noteworthy features in sections from the central region of the cystic floor.

The second brain displays no thickening or turbidity of the soft membrane. There was a marked edema and engorgement of the pial vessels. The gyri over the anterior region of the frontal lobes are small and atrophic. The vessels at the base of the brain are sclerotic. The cyst is located at the base. The depression is on the anterior pole of the left temporal lobe; the displacement, measured on the corresponding normal temporal lobe, is 4 by 3 by 2.5 cm. The cyst developed between the layers of the arachnoid; the inner sheet, although extremely thin, is nevertheless visible on the floor of the cystic cavity. The weight of the brain is 1,500 gm. The cerebrospinal fluid was clear and increased in amount.

Histologic sections show a delicate pia and a thin layer of flocculent arachnoid tissue; the large vessel, the artery of the sylvian fossa, has markedly sclerotic, excentric thickening of the wall containing cavity formation and cholesterin slits. Apparently there are no changes in the underlying brain tissue.

The patient was a man of 67 years who was admitted to the Cook County Hospital in coma. No history was obtained. It was learned that he had been drinking considerably since the death of his wife. A physical examination revealed the face somewhat reddened and swollen, a red line posteriorly along the hair line, absence of the patellar reflex, a suggestion of a Babinski on the right side. A diagnosis of erysipelas was made. The patient ran a septic temperature. Five days later the erysipelas had cleared up, but the patient's mental condition was very poor; he failed to understand or recognize any one. He was transferred to the Psychopathic Hospital; here he was irrational, talkative and restless; there was no response to treatment. The temperature was about 100 F. and continued so until death, which occurred the day following his transfer. The Wassermann reaction of the spinal fluid was negative. At the postmortem examination no fracture of the skull or changes of the dura were found.

These cysts probably resulted from inflammatory alterations in the leptomeninges; in the one instance there was

marked chronic thickening caused by alcoholism, in the other edema and hyperemia, presumably arising in the course of erysipelas. Adhesions resulted in obstruction to the outflow of the cerebrospinal fluid in circumscribed areas. The increase of fluid in such cases is to be explained rather by a continued flowing into these regions from the perivascular lymph spaces of the peripheral portions of the brain than by a secretion of fluid by the endothelial cells lining the cysts, as believed by some authors.

Feb. 12, 1917.

CHEMOTHERAPY OF TUBERCULOSIS

LYDIA M. DEWITT

Since the discovery of the tubercle bacillus, efforts have been made to discover a specific cure for the disease. When Koch first announced tuberculin to the world, it was believed that such a specific had been found. But time has shown that neither the old tuberculin of Koch nor any of its successors and modifications can be relied on to cure tuberculosis. Since the disease was first known, long before the discovery of its causative agent, drugs have been used more or less empirically and symptomatically for its treatment, but it is only within a very few years that any systematic study of chemotherapy of tuberculosis in the sense of Ehrlich has been attempted.

Within these few years, experiments have been made with copper, gold, arsenic, mercury and certain dyes.

In 1912, v. Linden and some of her co-workers reported the use of various copper compounds in the treatment of experimental tuberculosis in animals and also in human cases of the disease. They claimed that these copper compounds, especially a lecithin compound patented under the trade name "Lecutyl," lengthened life, increased weight, lessened fever, and in some cases apparently cured the disease. Numerous other reports followed, some confirming her reports and others showing quite opposite results. Corper, working in our laboratory, found that none

of the copper compounds used by him had any beneficial influence on the course of experimental disease in animals, while his analytical experiments showed that no considerable amount of the copper used was found in the tubercles. This might have closed the question of the use of copper in tuberculosis, but for the recent appearance of a large number of reports from Japanese investigators on the use of a copper compound suggested by Koga under the name cyano-cuprol. According to these reports, some beneficial results have been obtained with this remedy, but the claims are not too confident and the latest report which I have seen states definitely that cyano-cuprol is not a specific cure for tuberculosis and should be accompanied by all possible hygienic measures.

Gold.—The use of gold salts in tuberculosis was first announced in 1912 by a group of German investigators, who based their work on Koch's statement that gold cyanid inhibited the growth of tubercle bacilli in very strong dilutions, 1 to 2,000,000. After using gold cyanid and gold potassium cyanid, they combined gold cyanid with cantharidin which had been detoxicated by treatment with ethylenediamin. The resulting compound they patented under the trade name aurocantan. This was used both in animals and men. In animals it was found to prolong life, increase weight, lower fever and improve the general condition, especially encouraging the formation of connective tissue around the tuberculous tissue. For the last two years I have been working with these compounds of gold. My work is not yet finished, but so far no such beneficial effect has been observed and analyses have shown no specific affinity of tuberculous tissues for gold. Indeed, it has been noted that usually the guinea-pigs treated with the gold salts died earlier than the untreated controls and with a more advanced tuberculosis.

Arsenic.—The use of arsenic in the treatment of tuberculosis was investigated by Corper and Arkin with entirely negative results.

Mercury.—I have for about two years been investigating the use of various mercury compounds in the

treatment of experimental tuberculosis. My work is not yet finished, but so far, the results have been in the main negative.

Dyes.—Corper investigated the fat-soluble dyes but he found that they did not penetrate the tubercle, penetrate, stain nor kill the tubercle bacilli, nor affect beneficially the course of the disease. I tried the effect of some of the azo dyes and Lewis of the Phipps Institute has carried on a long series of investigations on various azo dyes and their derivatives, but so far no especially encouraging results have been published. I have also for some years been working on methylene blue and allied dyes and their derivatives. Methylene blue easily penetrates the tubercle, easily penetrates and stains the tubercle bacillus and has a strong inhibitory power over its growth in the test tube. Alone, however, it failed to cure the experimental disease in guinea-pigs and therefore large numbers of derivatives have been tried. An iodin compound and a mercury compound have seemed in the preliminary experiments to have some beneficial effect, though none of these compounds can be said as yet to have cured a single case of experimental tuberculosis in the guinea-pig.

These chemotherapeutic experiments are still being carried on along similar lines, but at the present time, it may be said, no specific remedy for tuberculosis has as yet been found. The most serious side of the question of chemotherapy is that most of the drugs which have been suggested as cures are definitely injurious and one can hardly too strongly condemn clinical experimenting in chemotherapy until animal experiments have shown the treatment to be innocuous and to have some definite beneficial effect on the course of the disease.

Feb. 12, 1917.

SPECIFIC PRECIPITINS FOR STREPTOCOCCAL PROTEIN

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Attempts to secure specific precipitation by the addition of immune sera to streptococcal proteins have been unsuccessful, owing to the inability to secure in solution the precipitinogens of the streptococcus bodies. Von Eisler was unable to demonstrate a precipitation, using broth or physiologic salt solution filtrates of streptococci or concentrated extracts made by dissolving streptococci in acids. Aronson secured a weak precipitation using 1 per cent. ethyldiamin extract of streptococcus bodies.

In attempting to secure a stable antigen for complement-fixation in streptococcal infections, it was found that streptococci readily dissolve in 5 per cent. antiformin which when neutralized makes a clear solution. In three rabbits injected with identical strains, such as antigen bound complement in dilutions as low as 1/64 of the anticomplementary unit. Precipitins were, however, not demonstrable and further concentration was attempted according to the method of Pick for securing a stable precipitinogen by precipitating with alcohol (95 per cent.) and purifying with ammonium sulphate precipitation. Such antigens do not give any of the protein reactions (Millon, Biuret, Adamkietwitz), yet are capable of binding complement in the presence of immune rabbit sera. Concentrates were also made from 2 months' old broth cultures.

These antigens were tested with the serum of three streptococcus-immune rabbits and normal rabbit serum, 6 scarlet fever sera, 6 sera from patients with chronic arthritis, and three normal sera. In no case was any precipitation secured.

From 0.1 to 2 c.c. of an antiformin antigen were injected into three guinea-pigs. Five c.c. injected into each animal three weeks later failed to produce any symptoms of anaphylaxis.

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TUBERCULOUS PERITONITIS AND PNEUMOPERITONEUM

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AND

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In initiating this investigation we had in mind especially the solution of the causes active in producing a thickening of the pleura, as noted in cases of pulmonary tuberculosis treated by means of artificial pneumothorax. Because of the difficulties encountered in studying this problem in experimental animals and the similarity between the serous linings of the pleural and peritoneal cavities, it was decided first to study the effect of pneumoperitoneum on the normal and tuberculous peritoneum and then, if possible, to apply these observations to the pleura.

It has been noted time and again, by such investigators as Kaufman,[1] who observed cirrhosis of the lung in normal dogs, Warnecke,[2] Klemperer[3] and others who made similar observations in cases of pulmonary tuberculosis that there is a definite fibrosis in both the normal and diseased lung under the influence of artificial pneumothorax. Kistler[4] explains this fibrosis, in part at least if not entirely, as due to the direct pressure occasioned by the pneumothorax.

1. Kaufman, H.: Beitr. zur klin. d. Tuberk., 1912, xxiii, pp. 57-61.
2. Warnecke: Ibid., 1910, xvi, pp. 171-82.
3. Klemperer, F.: Berl. klin. Wchschr., 1911, xlviii, p. 2285.
4. Kistler: Beitr. zur klin. d. Tuberk., 1911, xix, pp. 459-67.

Whether the air per se had any influence on the pleura or lung we were unable to find in the literature. The peritoneal cavity being encased in a flexible or elastic abdominal wall seemed also to present certain advantages in solving the latter question. We were also unable to find in the literature any observations where special attention had been paid to this point.

Our observations were, therefore, confined to solving the following points:

1. Does air per se have an appreciable action on the serous surfaces—pleural and peritoneal?

2. Does the injection of air per se have an appreciable effect on the rate of absorption of the air from the pleural and peritoneal cavities?

The reason for considering the latter point was because in pneumothorax it has been noted by Klemperer[5] that the absorption of the gas diminishes as the time of persistence of the pneumothorax increases and Rest,[6] in a good critical review of artificial pneumothorax, considered this an established fact.

3. Does air per se have an influence on tuberculous peritonitis? Is its use to be recommended or condemned?

It is of course an accepted fact among surgeons that simple laparotomy acts beneficially in tuberculous peritonitis and the air and light have been given the credit for this action by some observers. Mosetig von Moorhof[7] in 1893 began to use air, contending that this procedure kept the serous surfaces apart thus preventing adhesions and aiding the absorption of fluid, and since then even to the present day the Italian and French have advocated this treatment.

4. Is there any difference between the rate of absorption of air from normal serous surfaces and those affected by tuberculosis?

5. To explain, if possible, what difference, if any, exists between pneumothorax and pneumoperitoneum.

The experimental work was carried out on rats because of the ease in handling these animals for this

5. Loc. cit.
6. Rest, E.: Quart. Jour. Med., 1912-13, vi, pp. 259-92.
7. Moorhof, Mosetig von: Wien. med. Presse, 1893, xxxi, pp. 1-4.

purpose, it being impossible to use human beings satisfactorily for the major part of the investigations. The inflation produced by means of air injected into the peritoneal cavity was maintained by noting the time of absorption as indicated by the Roentgen ray and then refilling at definite intervals. The tuberculosis of the peritoneum produced in the rats resulted from the injection of definite amounts of a heavy emulsion of dead tubercle bacilli in sterile physiological salt solution. Dead tubercle bacilli were used for this purpose since they produce all the lesions obtained with living and have the advantage of not being influenced by the indefinite factors of growth of the bacilli or resistance of the rats to the infection — a definite number always duplicating in location and amount the tuberculosis produced.

The time required for the absorption of 20 c.c. of air from the peritoneal cavity of normal full grown rats and rats with tuberculous peritonitis produced by dead tubercle bacilli was found to be uniformly about three days, regardless of whether it was an initial inflation or whether the inflation had been kept up for four months by repeated injections of air and the time determined by Roentgen ray at the last injection.

The constant inflation of the peritoneal cavity by means of air by repeated injections at three day intervals for four months produced no visible changes in the peritoneum or abdominal organs of normal rats.

The intraperitoneal injection of air coincident with or shortly after the intraperitoneal injection of dead tubercle bacilli resulted in a more marked dissemination of the tubercle bacilli and tubercles resulting therefrom over the peritoneal surfaces and especially in the region of the diaphragm as compared to control animals not having been injected with air but receiving tubercle bacilli alone. In the case of the latter the bacilli were usually found in a well walled off individual focus which was surrounded by the omentum and in the vicinity of the spleen and greater curvature of the stomach.

The air inflation kept up for four months in rats receiving dead tubercle bacilli, also did not result in an appreciable thickening of the peritoneum.

After having established these facts regarding pneumoperitoneum and experimental tuberculous peritonitis it was thought advisable to further make some observations on pneumothorax to note if possible why there was a slowing of the absorption of the air after pneumothorax had been kept up for a long period of time.

Observations were made on a number of cases of pulmonary tuberculosis in which pneumothorax was kept up for a long period of time up to one and one half years and it was noted as previously stated by Klemperer[8] that the absorption of the air diminished as the time of persistence of the pneumothorax increased, thus pneumothorax differed from pneumoperitoneum. In the hope of throwing more light on the subject a series of patients having had artificial pneumothorax for varying lengths of time were given intrapleural injections of a solution of methylene blue and the rate of absorption gauged by the appearance of the stain in the urine. It is noteworthy that there was very little difference between the absorption of the methylene blue in cases of short duration and long standing artificial pneumothorax.

Wherein now lies the difference between conditions in the pleural cavity and the peritoneal cavity?

Since the pleura and peritoneum do not differ greatly in fundamental properties the air per se can not explain these differences. That there is an unmistakable and direct connection between the fibrosis of the lungs and the pressure exerted by the pneumothorax was pointed out by Kistler.[9] But whether this fibrosis per se affects the rate of the absorption of the gas in the pleura is still to be answered. It does not diminish the absorption of crystalloids, i. e., methylene blue. As a result of the above cited observations we are inclined to believe that the diminished rate of absorption is probably to be accounted for by the fact that we are dealing in the case of pneumothorax rather with a chamber, the rigid chest wall in which is enclosed the lung, which initially when pneumothorax is first established tends to reexpand and thus

8. Loc. cit.
9. Loc. cit.

by this tendency aids the rapid removal of the gas from the pleural cavity. Later on, however, as the pneumothorax is kept up on account of such factors as the fibrosis, etc., occurring in the lung, it tends to remain collapsed and thus of necessity would in itself diminish the rate of disappearance of the gas from the pleural cavity. On the other hand in pneumoperitoneum the conditions are entirely different; the pressure, which in the pneumothorax causes the fibrosis probably indirectly, is compensated by the flexible abdominal walls and thus is removed the possibility of any change in absorption rate of the gas even after pneumoperitoneum has persisted for a long time.

In conclusion we wish to express our appreciation to Dr. Imas Rice for aiding us in carrying out some of the experiments reported on.

March 12, 1917.

A COMPARISON OF THE AUTOLYSATE ANTIGEN AND MILLER'S BACILLARY ANTIGEN FOR COMPLEMENT FIXATION TESTS IN TUBERCULOSIS

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AND

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As a result of a comparative study made of the autolysate antigen[1] and Miller's bacillary antigen,[2, 3] using for comparison a number of monovalent autolysate and Miller's antigens prepared from the same strains of virulent human tubercle bacilli—1305, 1563 and 2417—and polyvalent antigens, autolysate and

1. Corper, H. J.: Jour. Infect. Dis., 1916, xix, p. 315.
2. Miller, H. R.: Jour. Amer. Med. Assn., 1916, lxvii, p. 1519.
3. Miller, H. R., and Zinsser, H.: Proc. Soc. Exper. Biol. and Med., 1916, xiii, p. 134.

Miller's, the latter obtained from Parke, Davis & Company representing eighteen different strains of tubercle bacilli, the following conclusions seem justified. These comparisons were made using 327 carefully studied and classified cases of nontuberculous and tuberculous individuals, both active and inactive.*

There is not a great deal of difference between the positive results obtained by means of these antigens, probably because the same basic substances are used in both antigens.

It is impossible by means of this test to absolutely differentiate active from inactive tuberculosis, the former cases giving a slightly higher number of positive reactions than the latter.

The autolysate antigen is to be preferred in performing these tests on account of the more transient nature of the results obtained with Miller's bacillary antigen and the difficulties encountered in obtaining a satisfactory antigenic unit.

It is advisable to run a Wassermann reaction on the same serum using one of the standard antigens (not reinforced or cholesterinized) and in the presence of such positive reaction to draw no conclusions from the tuberculosis test.

The positive complement fixation test for tuberculosis, in the absence of a positive Wassermann, is mainly of differential diagnostic value, and taken with other findings aids in making a definite diagnosis of tuberculosis.

March 12, 1917.

THE EFFECT OF TOLUENE ON THE BONE MARROW OF RABBITS

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In a study of the effect of toluene on the antibody production of rabbits by Hektoen[1] it was noted, as Kline and Winternitz[2] had pointed out, that the bone

* Appreciation is due Dr. W. A. Gekler for his kind assistance and the physicians of the Municipal Tuberculosis Sanitarium for their cooperation during the course of these investigations.

1. Jour. of Infec. Dis., 1916, xix, p. 737.
2. Jour. Exper. Med., 1914, xviii, p. 80.

marrow of the femur underwent marked changes and after several injections was more cellular. than that of normal rabbits. An effort was then made to study more carefully these changes as to the time and place of their appearance and the kinds of cells involved. Young rabbits were used of about a kilo in weight. They were injected subcutaneously every day for nine days with one cubic centimeter of toluene dissolved in one cubic centimeter of olive oil. One rabbit was killed every other day after the injections were begun until the eleventh day and the rest died or were killed at various times up to the 120th day. The marrow from the femur, tibia, humerus, ulna and radius was removed and fixed in equal parts of bichlorid of mercury and absolute alcohol, embedded in paraffin and stained with a combined Jenner-Giemsa stain and with hematoxylin and eosin. Sections were also made of spleen, liver and appendix, fixed in Zenker's fluid and stained with hematoxylin and eosin.

The greatest variations were found in the marrow of the femur, next in that of the humerus, while that of the tibia, ulna, radius, rib and spine varied much less. The marrow from the various bones of the same rabbit differed only in the degree of change, not in the kinds of cells involved. The increase in the number of cells became marked in the rabbit killed the day after the third injection, that killed the day after the second injection showing no more cells than the normal. Each successive rabbit showed a steady increase to that killed the second day after the ninth injection. In this rabbit the blood forming cells of the femur and humerus had entirely replaced the fat cells. From the second day after the ninth injection the number of cells decreased, and on the sixth day there would be about the same number as in the normal. From then on there were distinctly fewer than normally even after sixty to seventy days. As the number of cells decreased the fat did not return to any extent. The blood channels of the marrow became somewhat congested the day after the eighth

injection and continued so in each rabbit till the one killed the sixth day after the ninth injection.

As to the kinds of cells involved in the hyperplasia it would seem that the myelocytes rather than the cells of the red forming series played the chief rôle (Fig. 1). The nongranular and amphophile myelocytes were far in excess of any other kind of cell. They showed large vesicular nuclei with well marked nucleoli and definite perinuclear membrane. There was no proportional

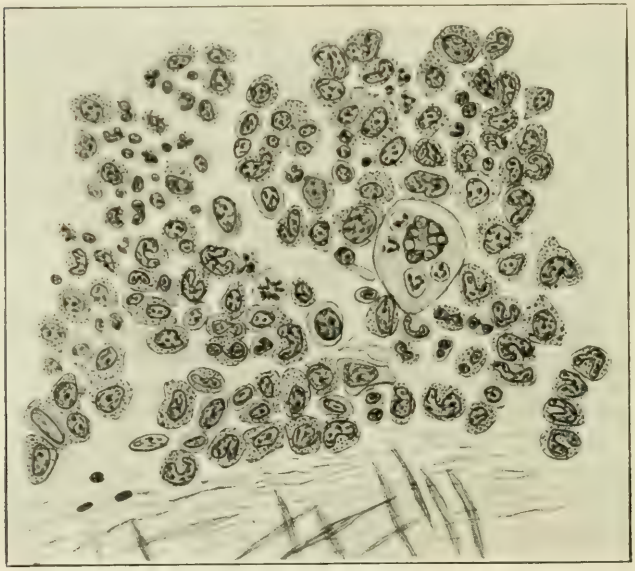

Fig. 1.—Drawing to scale by Dr. Leila Jackson of section of bone marrow of femur of rabbit killed after subcutaneous injection of 1 c.c. of toluene in 1 c.c. of olive oil on 10 successive days. Leishman's stain. The section shows the great proliferation of cells throughout the marrow, the absence of fat cells, the preponderance of granular myeloid cells, and the phagocytosis by the giant cells of polymorphonuclear leukocytes. (1/12 oil im. obj. Leitz, eye-piece 5.)

increase noted in the eosinophil myelocytes, basophil myelocytes, polymorphonuclear leukocytes or cells of the red forming series containing hemoglobin. The giant cells showed no constant increase or decrease over any other cells. Phagocytosis was well marked in them. From the first marrow examined to that

examined on the fourth day after the ninth injection the giant cells were found to contain in a great many cases one or more polymorphonuclear leukocytes with a clear zone around the enclosed cell. In most of these cases the nucleus of the giant cell seemed to stain rather diffusely. The increase in the number of karyokinetic figures was very slight after two or three injections.

The appendix, spleen and liver were unchanged except perhaps for a slight fatty change in the liver. There was no increase or decrease in the lymphocytes of the spleen or appendix and no myeloid metaplasia of the spleen. The spleen and appendix were treated with potassium ferrocyanid and acid alcohol for the demonstration of iron. There was no increase in the amount of iron, indicating that there had been no great destruction of red blood cells or else the blood pigments had not yet been changed to hemosiderin.

In another set of seven rabbits, weighing about a kilo and a half each, toluene was injected in the same way every day for seven days and the leukocytes and red cells counted on the second, fourth and seventh day during the injections to see if there might be a coincident increase in the hemal leukocytes. The leukocytes never went below 4,500 nor rose above 13,000 and did not vary constantly in either direction. The red count was also not noticeably affected. The differential count showed a slight decrease in the polymorphonuclear cells and increase in the mononuclears after one and two injections, but this decrease was not more than 9 per cent. The count was approximately normal on the seventh day.

SUMMARY

Repeated injections of toluene in rabbits cause a hyperplasia of the myeloid cells of the bone marrow and a phagocytosis by the giant cells of leukocytes, without a coincident increase in the cells of the circulating blood nor changes in the liver, spleen or appendix. This hyperplasia is quickly followed by a decrease of the cells below normal when the injections are stopped.

THE INFLUENCE OF PANCREATIC DIGESTION ON THE PROTEOLYTIC ACTIVITY AND THE NON-COLLOIDAL NITROGEN CONTENT OF THE BLOOD SERUM

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AND

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It is a matter of common knowledge that the amino acids are increased in the blood serum at the height of digestion. Abderhalden states that this increase in amino acids may be responsible for a positive reaction when his test for pregnancy is applied to the blood serum of an individual at the height of digestion. One of us found, in working with the Abderhalden reaction, that the inactivated serum control gives a negative result even if the blood is taken at the height of digestion. This apparent discrepancy led to a quantitative study of the non-colloidal nitrogen content and the proteolytic activity of the blood serum in the fasting state and at the height of digestion. For this work dogs were selected because of the ease with which relatively large amounts of serum can be obtained from these animals, and because dog serum closely resembles human serum so far as its proteolytic activity is concerned.

Apparently normal animals were used for our experiments. The fasting animals had received no food for twenty-four hours. These at the height of digestion were killed eight to nine hours after the ingestion of a relatively large amount of meat containing a moderate amount of fat. On postmortem examination in the case of the digesting animals absorption was found to be going on rapidly, as evidenced by the injection of the lacteals and the milky appearance of the sera, after centrifugalization of the

defibrinated blood. The animals were lightly anesthetized with ether and bled from the femoral artery under aseptic conditions, into a sterile flask containing glass beads. The blood was defibrinated by shaking the flask. It was placed into sterile tubes and immediately centrifugalized under aseptic conditions. The serum was drawn off and combined in a single sterile container to obtain a uniform mixture. Samples were removed and placed into three sterile tubes. Placental tissue, prepared according to the Abderhalden technic, was added to two of these tubes, one of which had been previously heated at 60 C. for two hours. Into another sterile tube was placed a volume of distilled water equivalent to the volume of serum used in each of the other three tubes and a quantity of placental tissue similar to that used in the serum tubes. This control was used to correct our results for the non-colloidal nitrogen yielded by the placenta, on incubation. A small quantity of toluol was added to the contents of each of the tubes. This was followed by incubation for forty-eight hours at 37.5 C., a glass stoppered bottle serving as a moist chamber. At the end of this period a bacteriological examination was made by smears and cultures on agar. The cultures and smears were negative in all instances.

At the end of the incubation period, 5 c.c. of serum were measured into a 250 c.c. volumetric flask, 75 c.c. of aluminum hydroxid cream were added and the flask filled to the mark with distilled water. The contents were well shaken and filtered. One hundred and twenty-five c.c. of the filtrate were transferred to Kjeldahl flasks and the nitrogen determined in the usual manner. The contents of the tube containing distilled water and placental tissue were treated in like manner. A total nitrogen determination was made on each of the sera. The results are shown in Table 1.

It will be seen that the blood sera of the animals at the height of digestion, in all cases, contained more non-colloidal nitrogen than the blood sera of the animals in the fasting state. The differences, however, were relatively small. On the basis of the total nitrogen an average increase of a little more than 1 per cent. was found. In only two cases (Dog 1, fasting

and Dog 5, digesting) was the non-colloidal nitrogen present in the serum after incubation with placental tissue, greater than that in the serum after incubation by itself. This increase was very slight. These results cast doubt on the idea that proteolytic enzymes are swept into the blood stream when rapid absorption takes place at the height of digestion, unless the unsaturated fatty acids absorbed simultaneously prevent their action.

The results on the inactivated serum and placenta seem to indicate that some of the non-colloidal nitrogen of the serum combines with the serum colloids during the heating at 60 C. This method of controlling the Abderhalden reaction may therefore be open to criticism.

TABLE 1

	Dogs	Fasting			At the Height of Digestion		
	No. 1	2	3	5	5	6
	Total Nitrogen						
	c.c.	mg.	mg.	mg.	mg.	mg.	mg.
Serum	2.5	23.5	24.3	25.2	23.0	21.0	24.0
	Non-Colloidal Nitrogen						
	Volume						
	c.c.	mg.	mg.	mg.	mg.	mg.	mg.
Serum	2.5	0.7	0.63	0.78	0.84	0.83	1.16
Serum + Placenta	2.5	0.82	0.62	0.77	0.84	0.99	1.14
Inactivated Serum + Placenta	2.5	0.66	0.53	0.66	0.91	0.79	....
Per cent. of Non-Colloidal Nitrogen on the basis of the Total Nitrogen		2.98	2.59	3.09	3.65	3.95	4.84
Average Percent. of Non-Colloidal Nitrogen			2.88			4.15	

In a second series of experiments, blood serum was obtained from four dogs at the height of digestion as previously described. The total nitrogen and the non-colloidal nitrogen of the serum were determined directly. Placental tissue prepared according to the Abderhalden technic, was added to some of the serum. This was incubated at 37.5 C. under toluol in a moist chamber, for forty-eight hours. Typical Abderhalden tests were carried out on 3 c.c. samples of serum. This is three times the quantity of serum ordinarily employed in the Abderhalden test. The incubation period was twice the length of that usually employed. Serum that had been heated to 60 C. for two hours (inactivated) plus placenta, and serum alone, were used as controls. These tests were performed in

duplicate. After an incubation at 37.5 C. for forty-eight hours, 10 c.c. of the dialysates were actively boiled with 0.2 c.c. of a 1 per cent. ninhydrin solution for one minute.

The strongest ninhydrin reactions were obtained in the tests on the active serum plus placenta. Those obtained in the plain serum control were next in the depth of color obtained. The least intense reactions were noted in the inactivated serum plus placenta controls. The non-colloidal nitrogen was determined in the serum which had been incubated with placental tissue for forty-eight hours at 37.5 C. in a moist chamber, under toluol. The analytical results are shown in Table 2.

TABLE 2

Dog No.	1	2	3	4
Volume of Serum		Total Nitrogen of Serum		
c.c.	mg.	mg.	mg.	mg.
2.5	20.45	22.30	23.1	27.6
	Non-Colloidal Nitrogen of Serum			
2.5	0.84	1.05	0.84	1.26
Non-Colloidal Nitrogen of Serum after Incubation with Placental Tissue				
2.5	0.84	0.96	0.91	0.96
Percent. of Non-Colloidal Nitrogen of the Untreated Serum on the Basis of the Total Nitrogen				
	4.10	4.30	3.63	3.47

This series of experiments was planned to magnify the results of any proteolytic activity of the blood serum as determined by the Abderhalden technic.

While the serum from each of the four dogs gave indication of a positive Abderhalden reaction, in only one case, that of Dog 3, was there any increase in the non-colloidal nitrogen of the serum after incubation with placental tissue. In two cases there was diminution.

CONCLUSIONS

1. Under the conditions of our experiments no increase in the proteolytic activity of the serum at the height of digestion was observed.

2. Positive Abderhalden tests obtained at the height of digestion in nonpregnant individuals probably depend on an increase in the amino acids in the blood serum.

3. The use of inactivated serum as control in the Abderhalden test may be open to criticism.

April 9, 1917.

THE SPINAL FLUID FINDINGS IN DISEASES PRESENTING SYMPTOMS IN COMMON WITH ACUTE POLIOMYELITIS

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This report deals with the spinal fluid findings in a series of non-poliomyelitic diseases, occurring in children, presenting symptoms similar to those present in acute poliomyelitis. These diseases include acute tonsillitis, pharyngeal diphtheria, pharyngitis with cervical adenitis, measles, bronchitis, bronchopneumonia, acute diarrhea, uremic conditions with coma and convulsions, hysteria with severe headache, coma of septic scarlet fever, chorea, epilepsy, toxic meningismus, epidemic cerebrospinal fever, muscular rheumatism, scarlet fever, postdiphtheritic paralysis, acute nephritis, and acute articular rheumatism.

The examination of the spinal fluid included an estimation of the pressure, appearance, total number and types of the cells present, globulin reaction according to the methods of Noguchi and Ross-Jones, presence of albumin by the Heller test, test for glucose with Haines solution, and cultures. The results are tabulated.

Poliomyelitic spinal fluid usually presents a normal pressure, absence of marked turbidity, a positive globulin reaction late in the acute stage and variable during the first week, almost invariably an increase in the number of leukocytes, from 15 to several hundred per c.mm., early consisting chiefly of the polymorphonuclear type and later changing to a predominance of the lymphocytes.

As a result of this study it is found that determination of the pressure, presence of albumin and glucose are of little value for purposes of differentiation;

TABLE 1.—SPINAL FLUID FINDINGS IN OTHER DISEASES THAN ACUTE POLIOMYELITIS

Case No.	Pressure	Appearance	Cells			Globulin		Albumin	Sugar reduction	Cultural Findings	Day of Disease	Disease
			Total	Polys	Lymphocytes	Ross-Jones	Noguchi					
1	–	C	3	0	3	0	0	0	0	.....	3d	Scarlet fever
2	N	C	1	1	0	0	0	0	0	.....	2d	Scarlet fever
3	N	C	4	.....		0	0	0	0	.....	4th	Dysentery
4	+ +	C	4	.....		1	0	0	0	.....	15th	Dysentery
5	N	C	5	.....		0	0	0	0	.....	2d	Scarlet fever
6	N	C	6	4	2	0	0	Tr.	0	.....	4th	Scarlet fever
7	N	C	2	0	2	0	0	Tr.	0	.....	5th	Muscular rheumatism and tonsillitis
8	–	C	3	0	3	0	0	+	–	.....	1st	Uremic coma and convulsions
9	N	C	8	.....		0	0	+	0	.....	1st	Acute tonsillitis
10	N	C	0	.....		0	0	0	0	.....	9th	Dysentery
11	N	C	0	.....		Tr.	0	+	0	.....	2d	Post diphtheritic paralysis
12	N	C	0	.....		0	0	0	–	.....	3d	Pharyngeal diphtheria
13	N	C	0	.....		0	0	Tr.	+	.....	3d	Pharyngitis, cervical adenitis
14	N	C	2	.....		0	0	0	+	.....	6th	Tonsillitis
15	N	S. Tr.	1	.....		0	0	–	0	.....	1st	Measles
16	N	C	2	.....		0	0	0	0	Neg.	2d	Measles
17	–	C	1	.....		0	0	–	0	Neg.	15th	Septic scarlet fever, nephritis
18	N	C	4	.....		0	0	Tr.	0	Neg.	2d	Hysteria with headache
19	–	C	1	.....		0	0	Tr.	0	Neg.	3d	Measles
20	–	C	2	.....		0	0	–	0	Staph. albus	2d	Measles
21	+ +	C	3	.....		0	0	+	0	Neg.	30th	Post scarlet fever nephritis in coma
22	N	C	6	.....		0	0	0	0	.....	.....	Acute chorea
23	N	C	10	.....		0	0	0	0	.....	.....	Acute chorea
24	N	C	1	1	0	0	0	0	0	Staph. albus	21st	Acute arthritis
25	N	C	3	1	2	0	0	–	+	.....	.....	Acute chorea
26	N	C	2	1	1	0	0	Tr.	0	Neg.	.....	Bronchopneumonia
27	+	C	2	2	0	0	0	Tr.	0	Neg.	.....	Epilepsy
28	–	S. Tr.	1166	.....		–	– –	– +	....	Diplococcus	2d	Epidemic meningitis
29	– –	C	4	3	1	0	0	–	0	Neg.	.....	Toxic meningismus, scarlet fever
30	–	C	3	1	2	0	0	+	+	Neg.	3d	Bronchitis and pharyngitis
31	–	C	3	2	1	0	0	+	0	Neg.	3d	Bronchopneumonia
32	N	C	1	0	1	0	0	Tr.	+ +	Neg.	2d	Measles
33	N	C	5	2	3	0	0	Tr.	+ +	Neg.	1st	Measles
34	+	C	2	0	0	0	0	Tr.	0	.....	1st	Diphtheria

albumin being present not only in poliomyelitic fluid but in many other diseases associated with a high febrile condition or with albumin in the urine. Glucose is also a variable constituent of the spinal fluid and its presence or absence of little if any significance. Cultural examination was negative except for the finding of meningococcus in the fluid from the case of epidemic cerebrospinal fever, and a case of measles in which staphylococcus albus was found; the former case had been treated as a case of bronchopneumonia, the true condition being found as a result of the spinal fluid examination carried out in the course of this study.

A determination of the globulin and the number and character of the leukocytes is of greatest value both for direct and differential diagnosis. In the non-poliomyelitic cases a positive globulin reaction was found in the case of meningitis, and a trace in the case of postdiphtheritic paralysis; in the former the presence of numerous diplococci, and in the latter the complete absence of leukocytes would immediately rule out poliomyelitis. An increase in the number of leukocytes is indicative of an inflammatory process involving the meninges, and only in the case of meningitis of this series was this condition present. The average number of leukocytes in the remaining thirty-three cases was three per c.mm., the actual counts ranging from 0 to 10 per c.mm. On the other hand, the average count in the fluid from eighteen typical cases of poliomyelitis, observed in a previous study, was 118 per c.mm., actual counts ranging from eighteen to 360.

Contamination of the spinal fluid with blood renders the findings unreliable as regards the globulin content and the number and character of leukocytes.

SUMMARY

In many acute diseases presenting symptoms in common with acute poliomyelitis, with the exception of those diseases involving the meninges, the globulin

reaction is negative, and no pathologic increase of the leukocytes occurs in the spinal fluid.

In thirty-three such cases an average of three cells per c.mm. was found present in the spinal fluid, the highest count being ten cells per c.mm.

April 9, 1917.

IS CITRIC ACID PRESENT IN NORMAL URINE?

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AND

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Urine of normal individuals, infants included, treated according to Salant and Wise, gives precipitates. The method of Salant and Wise is an application of the Denige's reaction for citric acid, to the quantitative determination of this acid. All such urines on suitable treatment yield pentabromacetone. With amounts of citric acid exceeding 10 mg. the pentabromacetone method gives good approximate quantitative results. Of the substances thus far tested, diacetic acid is the only one which, when added to urine, gives a precipitate with the pentabromacetone method when the controls do not. Thus far two substances were found giving a precipitate with the Denige's reaction, but no pentabromacetone. One, aconitic acid, the other a specimen of pyruvic acid (Kahlbaum), which having stood in the laboratory several years no doubt contained condensation products. It is of interest that tricarballylic acid does not give either of the two reactions. There seems to be a possibility that citric acid may be derived from hemopyrrol in the organism (Dr. Retinger).

The facts given speak very strongly in favor of the presence of citric acid in normal urine.

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PRECIPITIN PRODUCTION IN THE ALLERGIC RABBIT

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The serum of rabbits subject to distinct injections of more than one kind of serum or blood may come to contain many precipitins in a concentration that far exceeds the limits of quantitative specificity necessary for practical tests as usually conducted. It would seem that as the blood and serum used as antigens contain many different antigenic substances, some of which perhaps are present, though in small quantities, in all the species concerned, the biologic specificity of the precipitin reaction may become less pronounced, less sharply limited quantitatively, the higher the increased reactivity of the rabbit yielding the precipitin-serum. On this account the serum for practical precipitin tests should be obtained by specific immunization of suitable, previously unused rabbits. On the other hand, under certain circumstances it may be found desirable in order to produce antibodies that are not easily put forth, to use allergic animals.

While the injection of foreign blood or serum in a rabbit previously injected with some other blood or serum may call forth various precipitins in large amounts because of the many antigens in the materials which are injected into an allergic organism, it is also possible that in the allergic animal the course of immunization may have left the mechanisms of antibody-production in such state that they can be aroused again into the same activities as before by new but totally different antigenic stimuli, and possibly even by stimuli of nonantigenic nature. The experiments so far, however, in which efforts have been made to reawaken precipitin-production by means of antigens regarded as different from those already injected and by means of metallic colloidal suspensions have given negative results.

April 9, 1917.

PULMONARY FAT EMBOLISM—A CAUSE OF POSTOPERATIVE SURGICAL SHOCK *

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This report concerns the illness and alterations found in the bodies of three persons who had been operated on for umbilical hernia, cancer of the breast and bilateral fibrocystic mastitis, respectively.

Case 1 (167261).—A hotel clerk, 32 years of age, entered the Mayo Clinic on July 26, 1916, in the service of H. S. Plummer. He complained that ever since boyhood he had suffered the inconvenience of a large umbilical hernia. In 1913 he sought relief in an operation, but after two months a hernia occurred in the operation scar. He stated that the hernia was growing larger and gradually becoming more painful and tender.

Physical examination revealed a well-muscled, but very obese man, weighing 222 pounds, with a large postoperative ventral hernia. Aside from the hernia he presented no noteworthy clinical abnormalities. On three successive days the twenty-four hour output of urine was normal and the specimens, while containing a trace of albumin, contained no casts or cells. Fifteen minutes after subcutaneous injection of phenolsulphonephthalein the kidneys returned 110 c.c. of urine in two hours, there being 47 per cent. of the dye in the sample. The average systolic blood pressure for three days was 133 mm. Hg, and the diastolic, 86 mm. The blood contained 7,400 leukocytes and 80 per cent. hemoglobin. The temperature was always normal.

On Aug. 5, 1916, the operation was performed by Judd and Masson. A long transverse incision was made across the abdomen, the hernial sac was freed from its surrounding adhesions to the thick layer of subcutaneous fat, and a mass of the great omentum,

* For the complete report with illustrations see Bissell, W. N.: "Pulmonary Fat Embolism—a Frequent Cause of Postoperative Surgical Shock," Surg., Gynec. and Obst., 1917, **25**, 8-22.

approximately 15 cm. in diameter, was removed. On account of a wide diastasis of the rectus muscles the closure of the sac was made very difficult and during this part of the operation the patient became quite cyanotic; sufficiently so to cause the surgeons considerable alarm. The closure was completed, however, and the patient returned to his bed. He improved during the next twelve hours after proctolysis and hypodermoclysis. The operation was done toward evening; at its close the pulse rate was 118 and the quality was pretty good. During the course of the next day the cyanosis persisted and was accompanied by considerable dyspnea. This cyanosis and dyspnea partially subsided by the end of the first twenty-four hours and it seemed that the patient was on the way to recovery. During the course of the second day, however, the temperature rose gradually to 100.5 F., and late in the evening a mild delirium developed. The delirium grew more intense, and by the morning of the second day was associated with tremor and wild hallucinations of sight and hearing. The temperature gradually rose to 105 F. and with it the pulse rate increased to 140 per minute. During the second day the respiratory rate rose rapidly, breathing was attended with great effort and there were signs of consolidation of lobes of the lungs posteriorly. Death occurred within forty-eight hours of the operation.

The patient had offered the history that he had been employed as a bartender and up to three months previous to his appearance for treatment had been a moderately heavy user of alcoholics. Had similar clinical observations been made on a person dead of broken bones it is probable that the clinical diagnosis of fatty embolism would have been made, but with the remote history of alcoholism and physical signs of consolidation of lung lobes associated with a delirium characterized by hallucinations and tremor, the clinical diagnosis of lobar pneumonia and delirium tremens seemed logical.

The following necropsy protocol is presented in some detail to impress surgeons more forcibly with the possible extent of postoperative fat embolism:

This is the body of a very obese white man, apparently about 33 to 35 years of age, weighing well over

200 pounds. Lividity of the face, the neck, the lobes of the ears and the entire posterior aspect of the body is very marked. Elsewhere the skin of the body possesses the pallor of one dead from hemorrhage. The umbilicus is missing and at its level there is a recently made laparotomy wound 28 cm. long and surgically closed with interrupted silkworm-gut retention sutures and a continuous horsehair skin suture. Body heat is present in an elevated degree, even externally.

Scattered over the skin of the abdomen and thorax there are a few (eleven in all) bright red petechial hemorrhages. These hemorrhages are approximately equal in size, measuring 1 mm. in diameter. They are to be found only in the skin of the ventral part of the trunk.

On opening the body by the usual midline ventral incision it is noticeable that in the depths of the herniotomy wound there is a great deal of fluid fat mixed with a small amount of bloody serum. In the removal of the hernial sac a rather elliptical-shaped area, 28 cm. long and 20 cm. wide, in the thick subcutaneous fat has been surgically traumatized. The trauma is apparently minimal considering the size and nature of the operation, and there has been no bleeding. The abdominal fat measures 10 cm. through its thickest portion. A part of the great omentum has been removed by this operation; the remainder contains an enormous amount of fat. Scattered throughout the visceral and parietal peritoneum are many bright red petechial hemorrhages the largest of which measure 3 mm. in diameter. There are no other noteworthy abnormalities in the peritoneum.

There is a small persistent thymus in the upper anterior mediastinum. There are no abnormalities in either pleural cavity or in the pericardial cavity. The great vessels entering the root of the neck are severed, together with the trachea and esophagus. The entire thoracic content is reflected downward, the diaphragmatic attachments to the ribs and spine are cut, and the entire trunk is eviscerated except for the contents of the pelvis. By so doing, all of the viscera of the trunk can be placed on a pan across the thighs

and examination can then be conducted from behind without removal of organs from their relations to one another, and, at the same time permitting thorough examination of the large venous trunks of the body.

The lungs are quite similar. Scattered throughout the pleura of both are many bright red and fading dusky-pink petechial hemorrhages. The dependent portions of both lungs are mottled dusky-slate and dusky-pink color. An autopsy pan is thoroughly

Fig. 1 is representative of the amounts of fat observed in microscopic preparations taken from many places in the lungs in Case 1.

cleaned with soap and water and dried with clean dry towels. The right lung is carefully washed with running water, and without severing its attachments at the hilum the lower lobe is placed over the freshly cleansed and grease-free pan while the convexity of the lung lobe is cut with a thoroughly cleaned knife blade. Immediately there is an escape of a great amount of fluid blood, and as this blood runs over the

dry surface of the pan, an almost incredible amount of fat in the form of oil droplets is visible floating on the surface. The lungs contain not only a great deal of fluid blood but a great quantity of watery frothy material. The surfaces made by sectioning the lungs are everywhere very hyperemic. Many areas of slight consolidation are seen in the lung parenchyma as slightly elevated hyperemic areas of slightly granular appearance.

The fatty tissues are dissected from the inferior vena cava and the pericardial covering of the auricles. The inferior vena cava is greatly distended with blood and on incising it many fat droplets are visible on the surface of the escaping blood. The blood in the left auricle also contains countless small oil globules.

In the leptomeninges of the brain there is a great deal of watery material and a marked engorgement of all the blood vessels. The cerebrospinal fluid is greatly increased in amount but is perfectly clear and watery.

Aside from these descriptions and the lesions named in the anatomic diagnosis there are no noteworthy gross abnormalities in this body. The contents of the neck and the floor of the mouth were not removed for examination.

Fresh preparations of the top layer of blood running from the surfaces made by sectioning the lung and allowed to stand in a small bottle during the course of the examination, contain nearly as many fat droplets as red blood corpuscles.

Anatomic Diagnosis.—Marked obesity; recently-made unhealed and surgically-repaired large transverse umbilical herniotomy wound; absence of a part of the great omentum; many oil droplets in the blood contained in the lungs, the inferior vena cava, right and left auricle, right ventricle and in the large dural sinuses of the brain; disseminated petechial hemorrhages in the skin, peritoneum and visceral pleura (fat embolism); marked engorgement of all the large venous trunks of the body and the right auricular and ventricular chambers of the heart; marked bilateral pulmonary edema; marked bilateral disseminated bronchopneumonia; marked catarrhal tracheobronchitis; slight hyperplasia of the tracheobronchial

lymph nodes and the spleen; marked edema of the brain; marked postmortem lividity of the entire dependent portion of the body and of the root of the neck and lobes of the ears; coalescing petechial hemorrhages in the mucous lining of the greater antrum of the stomach, the duodenum, the cecum and rectum; marked cloudy swelling of the kidneys and myocardium; marked fatty changes in the liver and myocardium; slight varicosity of the superficial veins of the legs.

Case 2 (170641).—A married woman, 41 years of age, entered the Mayo Clinic on Aug. 26, 1916, in the service of W. A. Plummer. There were no details in her family or personal or menstrual history bearing on her complaint of right upper abdominal, cramp-like pain. She stated that since the birth of her 7 year old child she had suffered occasional attacks of this abdominal pain which necessitated the use of morphin. The spasms of pain were of sudden onset, usually lasted one half to two hours and never were followed by jaundice. In all, she had suffered five attacks, the last one occurring two weeks previous to this examination. The pains were never associated with eating and always radiated to the right shoulder blade. She could not recall that she had had fever with these pains. In addition, she called attention to a nodule in the right breast which had been growing since spring.

On physical examination she was found to be a rather stout, little woman, weighing 165 pounds. Her general health was apparently excellent. A palpable nodular and cystic condition was present in both breasts and there was distinct tenderness over the gallbladder area. There were no axillary enlargements. Examination of the urine revealed nothing abnormal. The blood contained 85 per cent. hemoglobin and the systolic blood pressure was 130 mm. Hg, diastolic 78 mm. Roentgenographic examination of the kidneys, ureters and bladder, did not reveal abnormalities. A clinical diagnosis of bilateral fibrocystic mastitis and cholelithiasis was made.

On August 30, four days after admission, C. H. Mayo enucleated both breasts by the conservative Warren operation, preserving the skin and nipples.

Under the same ether anesthesia he removed a thick-walled gallbladder filled with stones. The entire operation consumed but eighty minutes. Recovery from the anesthetic was normal. Within twenty-four hours the pulse rate rose to 120 per minute and the temperature rose from 97.6 F. to 101; some dyspnea and slight cyanosis developed and the patient became stuperous. During the third day the cyanosis increased and delirium followed. Before death the temperature rose to 103.4 and the pulse rate to 146 per minute. The clinical cause of death was given as surgical shock.

Clinically this death resembled both surgical shock and fat embolism. The rapid, running, easily obliterated pulse resembled shock. The dyspnea, cyanosis, delirium and fever resembled fat embolism. Dyspnea, cyanosis, and delirium, however, are also noted in surgical shock.

The necropsy was conducted four and one half hours postmortem in the manner outlined in the first case.

Anatomic Diagnosis.—Recently made and surgically repaired and drained wounds inferolateral to each breast and in the right rectus muscle; absence of both breasts and the gallbladder; moderate obesity; moderate bilateral disseminated fat embolism; fat droplets in the blood expressed from fresh cuts of lung lobes; fat droplets in the fluid material in either pleural cavity, in the tracheobronchial secretions, in the urine, and in the blood clots of the right auricle; disseminated petechial hemorrhages throughout the lining of the small bowel and in the lining of the greater antrum of the stomach; petechial hemorrhages in the mucous lining of the pelvis of the left kidney and in the visceral pleura of both lungs, throughout the peritoneum generally, in the trachea and main bronchi and disseminated throughout the visceral pericardium and the capsule of the liver; marked fatty changes in the liver; corset deformity of the liver and kidneys; slight bilateral hemo-hydrothorax; slight amount of fluid and clotted blood in the dependent portions of the peritoneal cavity; remarkable increase in body heat; moderate gas distention of the small bowel; mucohemotracheobronchitis; marked engorgement of

all the large veins of the body and of the chambers of the right side of the heart; marked general visceroptosis; atrophic striae gravidarum of the skin of the abdomen and thighs.

Case 3 (171631).—The last case report is of a woman 56 years of age entering the Mayo Clinic on Sept. 6, 1916, in the service of Logan. She complained of a tumor mass in the left breast which had been present for three years, accompanied for two years by a swelling in the left axilla. Her disorder was obviously a carcinoma of the breast with axillary glandular metastases. Physical examination revealed no contraindications to operation. She weighed 160 pounds, which was her normal weight, and there was no evidence of distant metastases of the cancer.

On Sept. 9, 1916, Dr. Beckman removed the left breast and axillary glands by Halsted amputation. The operation consumed seventy-five minutes. The patient recovered from the ether anesthetic very promptly and her pulse was of good quality. Very soon, however, the pulse rate increased rapidly and the temperature was subnormal. In spite of vigorous stimulation and application of external heat, she continued to have a subnormal temperature and the pulse was very rapid, irregular and difficult to count. There was no evidence of hemorrhage. After remaining in this condition for ten hours she died. The clinical cause of death was given as surgical shock.

The necropsy gave the following anatomic diagnosis: Large, recently made, surgically incised and repaired and drained wound of the left breast and axilla; absence of the left breast and the left axillary lymph nodes; slight surgical trauma to the left axillary vein; moderate bilateral disseminated pulmonary fat embolism; moderate bilateral hypostatic hyperemia and edema of the lungs; moderate bilateral hydrothorax; petechial hemorrhages in the mesentery of the small bowel and in the capsule of the spleen; pin-head sized petechial hemorrhages of the skin; moderate obesity; left apical fibrous adhesive pleuritis; moderate general anemia; marked engorgement of all the large venous trunks of the body; slight chronic diffuse nephritis—slight secondary contraction of the kid-

neys; marked cloudy swelling of the liver and kidneys; varicosed veins of the legs.

While the first instance cited was at no time clinically considered a condition of so-called surgical shock, it is reported to emphasize the severity of fat embolism in some instances of necessarily extensive surgical operations in a thick layer of subcutaneous fat. The instance of death following conservative amputation of both breasts and cholecystectomy may be criticized as not characteristic of surgical shock since this person had fever, yet the report is justified since the clinical diagnosis of surgical shock may be hazardous in most instances, as surgeons frequently offer this explanation under protest, and then only by process of exclusion, and pathologists, heretofore at least, have offered no adequate anatomic diagnosis.

The author[1] has observed large quantities of fat in the venous blood of persons with broken bones, in some instances almost incredible amounts, and Gauss[2] has demonstrated quite conclusively that oil droplets in the blood cause a remarkable increase in viscosity.

Warthin[3] demonstrated the effect of intravenous injections of oil on the arterial and venous blood pressure of dogs. By the pulmonary fat embolism so produced the passage of blood through the capillaries of the lung is greatly interfered with. There being no obstruction to the flow of blood through the peripheral arterial circuit, the greater portion of the circulating blood is accumulated in the venous system and as is commonly said, the patient bleeds to death into his own veins. Clinically, it is one of the criteria of surgical shock that the systolic arterial blood pressure is low; experimentally in animals pulmonary fat embolism causes a marked fall in arterial blood pressure and a corresponding coincident rise in venous blood pressure.

In the two instances of breast amputation reported, death was supposedly due to postoperative surgical shock—actually, there were no lesions found at

1. Bissell, W. W.: The Amounts of Fat in the Blood Stream of Persons with Broken Bones. Jour. Am. Med. Assn., 1916, lxviii, 1926-1927.

2. Gauss, H.: Studies in Cerebral Fat Embolism with Reference to the Pathology of Coma, Arch. Int. Med., 1916, xviii, 76-102.

3. Warthin, A.: Traumatic Lipaemia and Fatty Embolism, Internat. Clin., 1913, iv, 171-227

necropsy to explain death other than those produced by fat embolism, and in the lungs this fatty infarction was extensive.

It would seem reasonable to conclude that:

1. Many deaths clinically supposed to be due to surgical shock, may actually be due to pulmonary fat embolism.
2. Pulmonary fat embolism causes a lowering of arterial blood pressure and an elevation of venous blood pressure.
3. By simple methods pulmonary fat embolism is easily demonstrated at the necropsy table.

May 14, 1917.

IMMUNE REACTIONS IN GONOCOCCAL INFECTIONS AFTER THE INTRAVENOUS INJECTION OF SPECIFIC AND NONSPECIFIC SUBSTANCES

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When a suspension of bacteria or a pure protein solution, such as primary or secondary proteose solutions, is injected intravenously into an individual there occurs a clinical reaction quite similar in every instance regardless of the bacteria or protein solution injected. This reaction takes place in a normal individual as well as one suffering from an infection.

The reaction is characterized by a chill of variable severity coming on in twenty to sixty minutes after the injection. Coincident with the chill there is a marked decrease in leukocytes in the peripheral circulation as well as a drop in temperature. This condition lasts for about twenty minutes when the chill abates and the temperature of the individual gradually rises, reaching its climax in four to six hours. At this time there is usually a profuse perspiration, also a considerable increase in leukocytes in the peripheral circulation. The temperature gradually

returns to normal within twenty-four hours while the leukocytes gradually return to normal within forty-eight hours.

These reactions when properly regulated and timed have been successfully used in the treatment of gonococcal infections such as arthritis, epididymitis and acute prostatitis.[1] Good results with critical fall of temperature have been observed in typhoid fever and other infections.

A very striking feature of the therapeutic action in gonococcal infections is the fact that in most cases, where a good result is to be secured, there is a decided improvement in the patient within twenty-four hours following the reaction. This improvement is most marked following the first injection.

Bull,[2] using normal and typhoid immune rabbits, notices no decrease in antibodies in the first twenty-four hours following an intravenous injection of typhoid bacilli. Instead of this so-called negative phase he finds a marked increase of lytic substances up to twenty-four hours.

Teague and McWilliams[3] elaborated on Bull's work and conclude that the bacteriolytic power of normal and immune antityphoid rabbit serum is neither increased nor decreased by the intravenous injections up to the first twenty-four hours. However, the serum of a rabbit that has received only one or two immunizing injections shows a distinct but not a great increase in its bactericidal power at five and twenty-four hour intervals after such injections.

This work deals with the study of opsonins and bactericidal substances in patient's serum suffering from gonococcal arthritis. One series was treated by injections of gonococci and a second series received injections of primary or secondary proteose.

Irons[4] has found that the opsonic content of serum from patients suffering from gonococcal arthritis may fluctuate spontaneously and the massage of an affected joint results in very noticeable opsonin increase. Hence any change in antibody content which results

1. Culver, H.: J. A. M. A., 1917, lxviii, p. 362.
2. Bull, C.: Jour. Exper. Med., 1916, xxiii, No. 3, p. 419.
3. Teague & McWilliams, Jour. of Immunology, 1917, xii, p. 167.
4. Irons, E. E.: Jour. of Infect. Dis., 1908, v, p. 279.

from an injection which produces a chill might well be explained by the motion of the affected parts during the chill.

The bactericidal substances and opsonins were determined just before and twenty-four hours after each intravenous injection.

The bactericidal tests were made by means of the dilution method as well as by the number of organisms killed per unit of time by a standard amount of serum. Although there is considerable evidence to discount results obtained by the dilution method, in these experiments using so delicate an organism as the gonococcus, this method gives the most constant and best results and the results here reported were obtained by this method. The opsonins were tested for by means of the extinction method.

It is the usual condition, as has been noted by others, that the opsonin content as well as the bacteriolysin content of the serum of patients suffering from gonococcal arthritis is normal or below before any injections are given.

Within twenty-four hours after the first injection of either gonococci or proteose preparations there may be a distinct rise in bactericidal substances and opsonins; however, there is more apt to be no change or a fall in opsonin during this time while the lysin of the same serum may show an increase.

As far as can be determined by these experiments, primary and secondary proteose preparations stimulate antibody production for specific organisms in a manner not to be distinguished from those produced by the injection of the specific organisms themselves.

However, with very few exceptions there is a distinct fall or no change in both antibodies within twenty-four hours after succeeding injections. However, between injections, which is a three day interval, there is a variable rise in both opsonin and lysin. This makes an irregular step-like curve for both antibodies.

These antibody curves are similar in patients that are benefited and in the refractory cases.

Since there is an appreciable increase in antibody within twenty-four hours only after the first injection and that cases not favorably influenced present a

similar antibody reaction, it is difficult to see how the well being of the patient within the first twenty-four hours following an intravenous injection can be accounted for by the mobilization of antibodies alone. The slight increase in bacteriolytic substances during the twenty-four hours following the first injection may have something to do with the marked improvement often seen during this time.

May 14, 1917.

THE COMPARATIVE PATHOLOGY OF CANCER OF THE STOMACH

MAUD SLYE, HARRIET F. HOLMES AND H. GIDEON WELLS

A review of the literature shows that in all animals except man, carcinoma of the stomach is extremely uncommon and the recorded cases in the lower animals are here collected and discussed briefly. In animals with a rumen, or with a squamous cell-lined cardia, carcinoma of this tissue is observed much more frequently than in the glandular gastric mucosa. But four cases of carcinoma of the stomach of mice could be found recorded in the literature, all in the squamous cardiac portion. In 16,000 necropsies of mice dying natural deaths at all ages, in this laboratory, we have found two squamous cell carcinomas of the cardia, and one tubular pyloric carcinoma; the latter apparently resulted from the presence of a hair ball in the stomach. One gastric neoplasm, resembling closely a sarcoma, was also observed. Carcinoma of the intestines is also very rare in mice, the only case observed in the Slye stock being a squamous cell carcinoma arising in the external surface of a chronically prolapsed rectum. The significance of man's susceptibility to carcinoma of the stomach is not yet known, but probably it depends on the heat of his food, the condiments, or the chemical changes produced by cooking.

(The full report is published in the *Journal of Cancer Research*, July, 1917.)

May 14, 1917.

FOOD ACCESSORY FACTORS (VITAMINS) IN BACTERIAL CULTURE WITH SPECIAL REFERENCE TO HEMOPHILIC BACILLI

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Food accessory factors have been recognized for the higher animals (Hopkins, Eykmann, Funk, Osborn and Mandel, Moore and Jackson, McCollum, Stepp, Holst and Froelich); for certain lower forms, Drosophila (Loeb and Northrop); for the higher plants (Bottomley, Jones); and for bacteria (Lloyd).

These substances are necessary for the proper nutrition of the organism in addition to the proteins, fats, carbohydrates, and salts.

They act in very small amounts and probably by themselves (at least for certain bacteria) are not able to support growth. They are relatively heat stable.

For the growth of hemophilic bacteria pure hemoglobin is one factor and a second factor resides in foreign bacteria and fresh animal and plant tissue. To obtain maximum development both factors are necessary. Hematin alone will not support growth, but in conjunction with other bacteria living or dead, will do so. The similarity of the action of these two factors to the action of fat soluble substances A and water soluble substances B of McCollum is pointed out.

The mechanism of the action of such substances is not clear. The availability of iron in the hemoglobin may be the determining factor in the growth of hemophilic bacteria. The second factor or substance may act by rendering this element more available.

The multiplicity of vitamins is recognized by most investigators. Their mode of activity may be as varied. Their action in connection with hemophilic bacteria seems to center around the metabolism of iron.

The suggestion may be made that the activity of these substances in animals and higher plants concern or somehow control the metabolism of certain elements like iron, phosphorus, calcium, or iodin, as well as the protein metabolism.

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TRANSACTIONS OF THE CHICAGO PATHOLOGICAL SOCIETY

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VETERINARY MEDICINE IN AMERICA

PRESIDENTIAL ADDRESS

L. ENOS DAY

At the last meeting of the year just closed I was unable to be present. A short time afterward I was very much surprised to find in the morning mail a letter from our worthy secretary notifying me that I had been elected president of this society.

I take this opportunity to thank you for the honor which you have conferred on me. This honor is probably greater appreciated by me than by any other member of this society for the reason that there are only two veterinarians who belong to this scientific body. I feel that by electing me as president you not only have conferred an honor on me but on the veterinary profession as well; thereby bringing the two professions to a closer working relation.

It has been customary in the past for the president of this society to make an address at the first meeting after he is elected. I have been casting about for some time trying to decide on what subject it would be best for me to address you this evening. Many subjects have come to my mind. Legend records that a number of sailors were sailing in a life boat for weeks after their vessel was wrecked at sea. They were famishing for food and water. Finally they saw a boat rise at the horizon and coming in their direction. When the ship came sufficiently near they hailed it and asked for water. Those on board the boat told them

to dip down where they were. They did so and found that the water was fresh. They found that they were and had been floating in the mouth of a great river of fresh water for days. So I, like the shipwrecked sailors, will dip down where I am and speak for a few minutes on a subject which is attracting much attention at the present time, especially in veterinary circles, and is of necessity of interest to the medical profession because of the common interests brought about by the two professions in sanitation and the great field of prophylactic medicine by the demands of the present and future.

Veterinary education is comparatively young in the United States; its foundation and growth having been very much the same as that of medicine. The first veterinary college was established in New York City in 1858. This institution was organized under the name of the "American Veterinary College" by Prof. A. Liautard, a then recent graduate of the Alfort Veterinary College, Alfort, France. The college was owned and maintained by private individuals; receiving no outside funds for its support. The matriculation requirements were low, the course of study consisting of two years' attendance of about six months each, after which an examination was given and a diploma issued.

For a number of years applicants who presented themselves for entrance into this new institution of learning were few, and after graduation they naturally remained in the eastern states to practice their profession. Later, as the trend of immigration moved westward, veterinarians also followed in the wake. Through the knowledge disseminated by these trained veterinarians, farmers and stock raisers soon appreciated their skill, although their training would not suffice today, and the needs for the establishment of veterinary colleges in other parts of the country became apparent.

Early in the eighties the states of Ohio and Pennsylvania established a veterinary department in connection with their state universities; also the Chicago Veterinary College, a private institution, was established in

this city. Since that time numerous state and private institutions for veterinary training have been established. While it is true that all of these various institutions were founded on a two-year curriculum they served a purpose in the right direction, that is, as a foundation for better teaching and training.

In 1897 the American Veterinary Medical Association, which, as its name implies, is composed of veterinarians residing in various parts of America, felt the need of a higher professional standard. A resolution was passed requiring that accredited applicants for membership shall be graduates from veterinary colleges having a three-year graded course of at least six months each. This brought about the desired effect, as nearly all of the various veterinary colleges complied with the requirements. Later this body, feeling again the demands of progress in all scientific branches of education, required that a four-year graded course of at least seven months each should be given by accredited schools. The United States Civil Service Commission has kept pace with the American Veterinary Medical Association in its demands for applicants for veterinarians seeking positions with the federal government. As a result of these demands all veterinary colleges, whether state or private, have raised their entrance requirements and have changed their curriculum to a four-year graded course.

The veterinary profession from its inception in this country has been very active, especially along the lines of protecting the live stock industry from the ravages of contagious diseases. Not only has it been active in combating contagious diseases in animals but has been an important factor in the preservation of the public health by assisting in throwing a safeguard around the public through meat and milk inspection.

The veterinary profession in this country has been especially fortunate in having men in its ranks with a sufficiently broad vision who were able to see and convince others of the importance of preventing the spread of certain contagious diseases by radical means that cannot be used by the medical profession. While many

of you are perfectly familiar with most of these diseases, I will mention a few of them.

Contagious pleuropneumonia, a fatal contagious disease of cattle, made its appearance along the Atlantic coast early in the eighties. While this disease is not so highly contagious as some others, by 1890 it had spread as far west as this state. Steps were taken to eradicate the disease and by 1892 this was successfully accomplished. Since that time the United States has remained free from this scourge.

Texas fever, a disease of cattle transmitted by a tick indigenous to the southern states, claimed millions of dollars worth of cattle annually. This disease has been greatly reduced by rigid quarantine until at the present time it is confined to a few of the extremely southern states.

Foot and mouth disease, a highly contagious disease of bisulcates, has appeared in the United States on four different occasions, and in one of these outbreaks was disseminated, more or less, from the Atlantic to the Pacific. Infections were found in twenty-two states and in the District of Columbia; the states affected being the principal stock-raising states of the Union. Each outbreak was at once combated and successfully eradicated by radical measures. At the present time this destructive scourge does not exist within the United States.

These achievements alone, to say nothing of the activities along other lines of prophylaxis and sanitation, has given the people generally confidence in the veterinary profession, and the demands gained by this confidence are constantly increasing.

As stated before, much has been done to raise the standard of veterinary education, yet it has not reached the desired point of perfection. The time is opportune for a modern, well-equipped veterinary institution in this state, preferably located in this city. Since so many branches of veterinary science are so closely associated in the study of human pathology, serology and prophylaxis, a department of veterinary science could be established in connection with a college of human medicine with advantage. Investigations show

that animals of various kinds are an important factor in the transmission of many of the diseases to man. Since so many animals are either carriers of diseases or are affected with the same diseases as man, it appears to me that by establishing an up-to-date, well-equipped department of comparative medicine in connection with one of our first-class medical institutions we would be able to meet the above demands.

One of our members, Dr. D. J. Davis, in an article read before the Quarterly Centennial of the University of Chicago last year, entitled "On Certain Relations of the Lower Animals to Human Beings," mentions more than twenty different animals and parasites which play some part in transmitting or disseminating diseases in man.

After these few brief facts stated to you tonight, I feel that you will bear me out in the belief that the time is ripe for such an institution. It is my sincere hope that these remarks, humble as they may be, will fall on fertile soil and bring forth fruit; and that the time may be near when Chicago can boast of the best appointed department of comparative medicine and research laboratories in North America in connection with one of her splendid universities.

Oct. 8, 1917.

ALLERGIC PHENOMENA FOLLOWING INTRAPORTAL INJECTIONS

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It was thought because of differences between portal blood in ferment, carbon dioxid tension, and rate of circulation, and also because the blood goes to the liver, an organ rich in proteolytic ferment which is interposed as a buffer between the intestinal tract and the peripheral blood stream, that protein substances injected into the portal blood might cause atypical reac-

tions in the allergic sense as compared with injection into the peripheral blood.

This work was undertaken to determine:

1. Whether or not animals could be sensitized by portal injection of foreign proteins.

2. If sensitized by this type of injection whether or not anaphylactic shock could be produced by subsequent injections via the same route.

3. Whether or not an animal could be sensitized by portal injection and shocked by peripheral intravenous injection.

4. Whether or not an animal could be sensitized by peripheral injection and shocked by intraportal injection.

5. If differences in the sensitizing and shock doses necessary to produce the reaction could be detected when using the portal or peripheral circulation as the place of injection.

Young guinea-pigs were used because of the sensitiveness of these animals to anaphylatoxin. Human serum was used as antigen and introduced either intraperitoneally or intravenously. All shock doses were given intravenously. The results of experiments can be seen in the accompanying table.

CONCLUSIONS

1. Guinea-pigs may be sensitized by intraportal injections of human serum.

2. Anaphylactic shock may be evoked after the usual latent period for this animal by subsequent intraportal injection.

3. Guinea-pigs may be sensitized by intraportal human serum injections and shocked by peripheral intravenous injections.

4. Conversely, guinea-pigs may be sensitized by intraperitoneal injections and shocked by intraportal injections.

5. Larger doses are necessary to produce anaphylactic shock in guinea-pigs when the shock dose is administered intraportally, irrespective of the method of administration of the sensitizing dose.

6. Passive anaphylaxis may be transmitted to a guinea-pig by way of the portal system and the pig may be shocked by portal or peripheral injections. Here again, however, larger doses seem necessary to produce shock when administered by the portal system.

7. Human serum will sensitize and produce anaphylactic shock in the guinea-pig. It is, however, not without toxic effect on nonsensitized guinea-pigs as shown by the fact that 1.5 c.c. intrajugularly caused death in four minutes with symptoms of anaphylactic shock and the same amount intraportally produced toxic symptoms but not death.

Oct. 8, 1917.

Group	Pig	Sensitizing Dose	Portal of Entry	Shock Dose	Portal of Entry	Result
	1	0.002	Intraportal	...	.....	Died in three minutes
	2	0.005	Intraportal	...	.....	Slight shock symptoms
	3	0.002	Intraperitoneal	0.2	Intraportal	Slight shock symptoms
	4	0.002	Intraperitoneal	0.2	Intraportal	No shock
1	5	0.002	Intraperitoneal	0.2	Intraportal	No shock
	6	0.002	Intraperitoneal	0.2	Intrajugular	Slight shock
	7	0.002	Intraperitoneal	0.2	Intrajugular	Slight shock
	8	0.002	Intraperitoneal	0.2	Intrajugular	Slight shock
	9	0.002	Intraportal	0.5	Intrajugular	Death in four minutes
	10	0.002	Intraportal	0.4	Intrajugular	Death in four minutes
2	11	0.002	Intraportal	0.3	Intrajugular	Death in five minutes
	12	0.002	Intraportal	0.2	Intrajugular	Slight shock
	13	0.002	Intraportal	0.5	Intraportal	No effect
	14	0.005	Intraperitoneal	0.5	Intrajugular	Death in two minutes
	15	0.005	Intraperitoneal	0.4	Intraportal	No effect
3	16	0.005	Intraperitoneal	0.6	Intraportal	No effect
	17	0.005	Intraperitoneal	1.0	Intraportal	Marked reaction, recovery
	18	0.005	Intraperitoneal	1.5	Intraportal	Death in twenty minutes
4	20	0.2*	Intraperitoneal	1.0	Intrajugular	Marked shock, recovery
Passive	21	0.2	Intraperitoneal	1.0	Intraportal	Slight shock
anaph-	22	0.2	Intraportal	1.0	Intrajugular	Marked shock, recovery
ylaxis	23	0.2	Intraportal	1.0	Intraportal	Slight shock
	24	0.002	Intraportal	0.4	Intrajugular	Marked reaction, recovery
	25	0.002	Intraportal	0.5	Intraportal	No effect
	26	0.002	Intraportal	1.0	Intraportal	Slight reaction
5	27	0.002	Intraportal	1.5	Intraportal	Marked reaction
	28	0.005	Intraperitoneal	0.4	Intrajugular	Death in five minutes
	29	0.005	Intraperitoneal	0.5	Intraportal	Slight irritation
	30	0.005	Intraperitoneal	0.8	Intraportal	Death in twenty minutes
	31	0.005	Intraperitoneal	1.0	Intraportal	Death in thirty minutes
	32	1.5	Intraportal	...	.....	Appeared toxic, recovered
Con-	33	1.5	Intrajugular	...	.....	Death in four minutes
trols	34	1.0 salt sol.	Intraportal	...	.....	No effect

* Sensitized serum from Pig 19 sensitized as were Pigs 14 to 18.

BACTERICIDAL ACTION OF GLYCEROL

WITH SPECIAL REFERENCE TO MICROCOCCI FOUND IN THE TISSUES OF POLIOMYELITIS

GEORGE MATHERS

AND

GEORGE H. WEAVER

It is our purpose at this time to briefly report the results of a few experiments made to determine the action of glycerol on micrococci isolated from the tissues of the central nervous system in poliomyelitis. The organisms used in this work included two strains each of poliomyelitic cocci, hemolytic streptococci and streptococcus viridans and one strain of pneumococci.

When these bacteria were grown for twenty-four hours on blood agar and suspended in sterile 50 per cent. glycerol they refused to grow after about three weeks. The pneumococcus was less resistant than the others, dying in about two weeks. One strain of the poliomyelitic coccus remained alive for thirty days. The same bacteria were grown on slants of blood agar and after twenty-four hours covered with sterile 50 per cent. glycerol and placed in the refrigerator. From these tubes cultures of all the bacteria were obtained three months after the glycerol was added. Furthermore, in two instances poliomyelitic cocci in the glycerinated spinal cord tissues of two fatal cases of poliomyelitis were found to be viable after a period of fifteen months. In view of these results it seems probable that the micrococci associated with poliomyelitis, similar to the virus of the disease, are markedly resistant to the bactericidal action of glycerol.

Oct. 8, 1917.

HISTOLOGIC DEMONSTRATION OF MICROCOCCI IN POLIOMYELITIC TISSUES

GEORGE MATHERS, L. HEKTOEN

AND

LEILA JACKSON

Many observers by the use of cultural methods have been able to demonstrate pathogenic micrococci in the tissues of the central nervous system of fatal cases of poliomyelitis. It seemed of interest to determine whether similar coccal forms are demonstrable microscopically in the central nervous system in poliomyelitis as it occurs in different places. Accordingly fixed poliomyelitic material was obtained from various sources, and these tissues, mostly pieces of spinal cord, have been studied. A more lengthy report of this work has appeared elsewhere.[1]

In all, material from 57 cases of poliomyelitis occurring in different parts of the country have been studied. Except in a few instances, changes characteristic of this disease were present most markedly in the gray matter, particularly the anterior horns. Definite coccal forms were found rather easily in sections showing poliomyelitic changes. They were single, oftener in pairs, occasionally in small clumps, usually outside but also within cells. They were located in the gray matter, in the walls of the blood vessels, in perivascular and other filtrates and in the hemorrhagic areas; they were also found in the meningeal infiltrations.

These cocci corresponded in general as far as shape, size and staining by Gram's method were concerned, with the cocci recently isolated in cultures of the tissues of the central nervous system in poliomyelitis. No other microbic forms were found in these tissues.

1. Jour. Inf. Dis., 1918, 22, p. 89.

It seems probable then that micrococci occur with great regularity in the central nervous system in epidemic poliomyelitis and their presence in these tissues is not explainable as due to accident or contamination.

Oct. 8, 1917.

STUDIES IN LOW BLOOD PRESSURES ASSOCIATED WITH PEPTONE SHOCK AND EXPERIMENTAL FAT EMBOLISM

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SUMMARY

1. In peptone shock there is a marked, precipitate fall in arterial pressure. At the same time there is a fall in venous pressure.

2. In experimental fat embolism, (*a*) the fall in arterial pressure is always gradual; (*b*) approximately 1 cubic centimeter of oil for each pound of body weight must be injected before there is produced a lasting fall in arterial pressure; (*c*) it makes only slight difference whether this amount is injected in small quantities at a time or in relatively large doses; (*d*) when the arterial pressure begins to fall, but not till then, the venous pressure rises.

3. In peptone poisoning, unless an overwhelming dose has been given, the animal will almost always recover, if the arterial pressure can be kept above the danger zone, or can be prevented from remaining for too long a time within that zone. This can usually be accomplished by the induction of dyspnea. In experimental fat embolism, a lasting fall in arterial pressure which may be comparatively small at the beginning, usually increases progressively and the animal dies within a few hours, in spite of dyspnea, which will also produce a rise in arterial pressure in this condition.

4. In experimental fat embolism, apnea frequently develops, sometimes even before the blood pressure has begun to decline. As a tentative explanation of this it is suggested that the toxic effect of ether may be augmented in fat embolism.

Nov. 12, 1917.

THE DISTRIBUTION OF MENINGOCOCCI IN THE UPPER RESPIRATORY TRACT OF CARRIERS *

RUSSELL D. HERROLD

In an examination of ninety-three meningococcus carriers, a comparison was made of the frequency of positive cultures from the nasopharynx with their frequency from other parts of the upper respiratory tract. Cultures were made of the nasopharynx, the tonsils, the anterior superior nares, and the sputum. The smears from these parts were inoculated on plain blood agar plates and all cultures diagnosed as positive were agglutinated in a dilution of 1 : 100 or higher of a polyvalent antimeningococcus serum, control tests with normal horse serum giving no agglutination.

The conclusions drawn from the observations are, that the nasopharynx is the most common seat of meningococci in carriers, but the carrier state persists longer the wider the distribution of meningococcus in the upper respiratory tract, and also that the number of positive cultures from other sources than the nasopharynx seems sufficient to warrant the taking of cultures from other parts than only the nasopharynx.

Nov. 12, 1917.

* The complete article appeared in *The Journal A. M. A.*, 1918, 70, p. 82.

CONGENITAL FALSE RIGHT DIAPHRAGMATIC HERNIA

REPORT OF A CASE WITH NECROPSY *

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Interest in diaphragmatic hernias has been stimulated since the x-ray has so facilitated the recognition of the condition. The defect is not unusually rare, but owing to the difficulty of correctly interpreting the physical signs until just recently the diagnosis has been but seldom made. In 1908, Arnsperger[1] stated that, up until that time, the conditions had been recognized in not more than ten instances during life. H. Z. Giffin[2] of Rochester, Minn., in 1912, stated that 650 cases of diaphragmatic hernia had been reported, and that antemortem diagnosis had been made in not more than fifteen instances. The malformation is undoubtedly much commoner than the number of instances reported would lead one to suppose, for, occasionally, hernias of a most extensive type give rise to no symptoms, and have been found while operating for some entirely different disturbance, or most often at necropsy, where death may have been due to other causes, or to incarceration or increased intrathoracic pressure, due to the hernia itself.

Diaphragmatic hernias according to Vogel[3] may be classified into three groups:

I. True Hernias.

(A) True congenital hernias in which pleura and peritoneum form a sac, the muscular and tendinous layer of the diaphragm being absent.

(B) True acquired hernias.

(a) True typical acquired hernias with a ring originating at one of the natural foramina.

(b) True atypical acquired hernias with the ring developing in a situation other than at the natural foramina.

1. Arnsperger: Deutsch. Arch. f. klin. Med., 1908, 92, 88.
2. Giffin, H. Z.: Ann. of Surgery, 1912, 55.
3. Vogel, K. M.: Amer. Jour. of Med. Sc., 1913, 145, pp. 206-219.

II. False Hernias.

(A) Congenital false hernias through a congenital defect.

(B) Acquired false hernia due to traumatic perforation of the diaphragm and either,
  (a) Acute, or
  (b) Chronic.

III. Diaphragmatic eventration due to a relaxation of the diaphragm, and involving either an entire half or localized in the form of a diverticulum. Eventration is simply elevation of the diaphragm, a doming up of one or both halves, usually congenital.

Of the congenital hernias, the false type, according to Leipman,[4] are by far the commonest and make up 87 per cent. of all such hernias. Of 433 examples of diaphragmatic hernia collected by Grosser and Thoma, 232 were congenital and 181 acquired. Livingston,[5] in 118 reported instances, tabulated these findings:

Right side	18
Left side	83
Central	4
Double	2
Diaphragm totally absent	1

Eppinger,[6] in 1911, made this classification among 635 instances of diaphragmatic hernia:

	Right Side	Left Side
Hernia vera	21	53
Hernia spuria	34	527
Eventratio	2	15

The false congenital hernia results from an imperfect development of the diaphragm, so that an opening permitting free communication between the thoracic and abdominal cavities exists from birth. This defect is most commonly present on the left side, in the space between the pars costalis and pars lumbaris of the diaphragm. Gössnitz,[7] studying in comparative anatomy, has demonstrated conclusively that this area is the last portion of the diaphragm to be closed. He

4. Leipman: Arch. f. Geburtsh., 1903, 68, p. 780.
5. Livingston: See Holt, Diseases of Infancy and Childhood, p. 119.
6. Eppinger: See Arch. Int. Med., 1916, 17, pp. 221-227.
7. Gössnitz: Inaug. Dissert., Jena., 1903.

says small defects invariably occur here. The size of the defect may vary from a tiny region to one involving the whole left or right diaphragm. Klebs reports such a defect in a child, who lived six years. The size of the congenital defect then depends on the degree of arrested development. Defects on the right side are very unusual and are said to be small.

Of the various theories advanced to explain the influences operative during intra-uterine life in restricting the normal closure of the diaphragm, that given by Laterjet and Jaricot[8] is perhaps the best. This theory, namely, that the portion of the diaphragm last to close is the most poorly vascularized, explains the preponderance of left-sided hernias. Any degree of abnormal pressure here would cause nutritional disturbance and a consequent arrest of development. The liver serves as a protective agency for preventing disturbances of development on the right side. Diellen and Knierim,[9] in 1910, reported the first example of right-sided hernia correctly diagnosed antemortem.

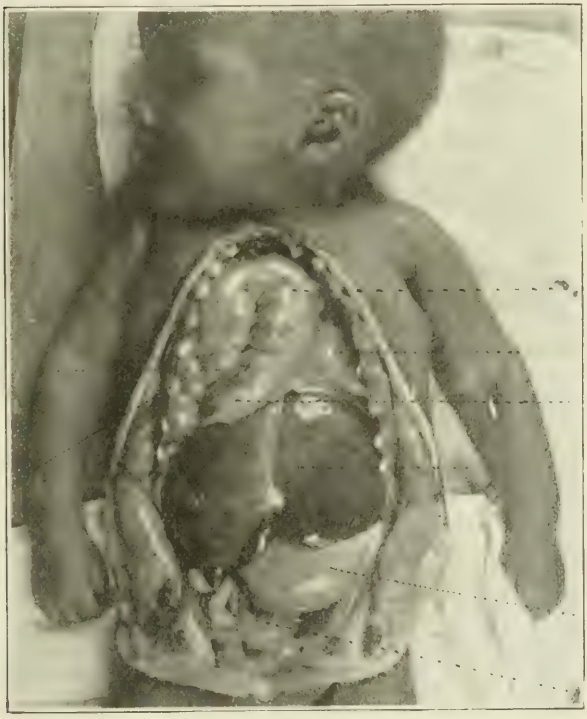
The content of these false congenital hernias may be anything in the abdomen. Of the hollow viscera, the stomach, then colon, then small intestine, are most frequently involved, while of the solid viscera, omentum is first in frequency, then liver, spleen and pancreas.

Incarceration occurs in about 15 per cent. of the patients, even though the ring is usually large. Such factors as torsion, taking of large quantities of food or fluid, increased intra-abdominal pressure caused by vomiting, straining at stool, parturition, falls on the abdomen, or contusions and adhesions, forming and interfering with peristalsis, bring on this condition.

The subject of this report of right sided congenital diaphragmatic hernia, was a female negro child, 3 months old. It was brought to the hospital by its mother, with the complaint of continuous crying, worse at night; vomiting, independent of meals; frequent stools, and a cough. The onset of the above occurred suddenly, three weeks before entrance to the hospital, at which time the child screamed

8. Laterjet and Jaricot: Bibliographie Anat., 1909, 18, 22.
9. Diellen and Knierim: Berl. klin. Wchnschr., 1910, 25, p. 1174.

out, crying steadily for three hours, until exhausted, then fell asleep to again suddenly awake, screaming violently. This condition gradually increased in severity. The child was breast fed and gained steadily in weight till the onset of this trouble, when it refused to nurse most of the time. Another child died of congenital deformities, otherwise, the family history is negative. The objective findings in the



thorax, were greater expansion on the left side of the chest with pronounced vocal fremitus and râles, the latter heard also over the right lung posteriorly. These were coarse, both inspiratory and expiratory. There was dyspnea and relatively little air passed into the right lung. Over the entire right chest in front there was marked tympany. The temperature was 101.2 degrees with both the pulse and respiration correspondingly increased. The child still was irritable. On account of the marked tympany found in percussing the

chest a roentgen-ray plate was taken. One could see the shadows present, and the photo, made of the chest contents after removal of the breast-plate will serve to explain these shadows. The child lived only forty-eight hours after entrance to the hospital.

At the necropsy the chest was distended, thickest and bulged out on the right side above. The abdomen was slightly retracted, but there were no deformities externally. A glance at the accompanying photograph shows how low the liver and stomach are pushed into the abdomen, and the presence there of only the rectum and that portion of the large bowel, distal to the splenic flexure. The proximal portion of the large bowel, the entire small bowel with a portion of the pancreas, passes through a defect in the right arch of the diaphragm, capable of admitting three finger tips. This defect is a little more to the right and front than the central portion. Roughly it involves the entire right lobe of the central tendons. It has no relation with the natural foramina of the diaphragm. The transverse colon, greatly distended, presents itself when the sternum is removed, while beneath this lies coiled the entire small bowel, likewise distended with its mesentery and a portion of the pancreas. The right lung is partially collapsed, the left enlarged to take on itself the function of the right. The heart is pushed far to the left. There is no pleuroperitoneal sac surrounding the intestine, nor is there evidence of strangulation, volvulus or adhesions. The only constriction is where the descending colon passes through the defect in the diaphragm at about the splenic flexure. Above this, the whole intestine is markedly distended, while distal to it normal descending colon is present. No change exists elsewhere in any of the organs of the body and death is accounted for by a marked increase in intrathoracic pressure with a beginning bronchpneumonia.

Nov. 12, 1917.

10. Giffin, H. Z.: reference cited.
11. Balfour: Ann. of Surg., January, 1916.
12. Grulee: International Clinics, Phila., 1915, 25, s. 11, 100.
13. Grandy: Jour. A. M. A., Chicago, 1915, 69, 1237.
14. Davis: Internat. Jour. Surg., N. Y., 1915, 27, 120-122.
15. Parker: Medicine, 1901-1907, p. 446.
16. Bailey and Smith: Text Book on Embryology.
17. Cunningham: Text Book of Anatomy.

THE VIRULENCE OF TUBERCLE BACILLI ISOLATED FROM THE SPUTUM

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The tremendous importance of the expectorated sputum and its associated droplet discharged during coughing and sneezing, in the dissemination and spread of tuberculosis, is known to all of us. There are, however, questions confronting us, of equal importance, which await sufficient experimental evidence for a definite answer. One of these, which was pointed out by Theobald Smith,[1] in his recent Mellon lecture, as being still unsolved, was the lack of conclusive proof of reinfection from a primary childhood infection or superinfection from without. There are equally good men (all without conclusive scientific evidence) on either side of this question. The other, whether the tubercle bacilli in the sputum are all virulent (or pathogenic) or not.

Robert Koch erred in his observations when the question of virulence confronted him. He for a long time did not see the difference between the human and bovine tubercle bacillus. The excellent observations of Theobald Smith, however, left no doubt of this difference. On account of the lack of information on the different types of tubercle bacilli, the observations made before 1898 were all unsatisfactory, especially with regard to the comparative virulence of bacilli harbored in the same type of animal and man. Smith,[2] however, made his emulsions for inoculation rather crudely, "equal in density to that of a bouillon culture of typhoid bacilli 20 to 24 hours old, and nearly as homogeneous."

He noted a sharp distinction between human and bovine bacilli in rabbits, the former being almost

1. Smith, Theobald: Jour. Am. Med. Assn., 1917, 68, 669-674 and 764-769.
2. Smith, Theobald: Jour. Exper. Med., 1898, 3, p. 451-511.

innocuous to this animal, while the latter caused generalized tuberculosis and death; but no data was obtained on the relative virulence of different human or bovine strains, in spite of the fact that he pointed out in a paper read before the American Climatological Association in 1898[3] (the same year), that the number of bacilli are of tremendous importance, lack of consideration of which invalidated Arloin's conclusions that surgical and skin forms of tuberculosis harbored avirulent, while pulmonary forms harbored virulent bacilli, deduced by the injection of infected tissues. Vagedes,[4] Lartigau,[5] Veszpremi,[6] and Dorset[7] all fell into the same pitfall, in that the amounts injected were crudely measured, and in most cases the rabbit was used as test animal, which proved in later experiments to be unsatisfactory. In general, they concluded that there was a difference in virulence of bacilli derived from similar sources, and some of these authors saw a relation between the virulence of the bacilli in animals and the course of the disease in man. Fraenkel and Baumann[8] were the first authors to prove that rabbits, rats and mice were unsuitable for virulence tests, for which they chose the guinea-pig.

Although their paper lacked scientific accuracy in many respects, they approached more nearly the actual state of affairs existing. They found that the virulence of 30 cultures of tubercle bacilli isolated from the sputum lay between one 1,000 millionth and one 100,000 millionth of a milligram (their paper is not entirely clear as to this amount). Reasoning by analogy with *B. prodigiosus*, they figured that there was 1 bacillus in the highest dilution given, although they had no way to prove this. Marmorek[9] was the first author to especially lay stress on the distribution of

3. Smith, Theobald: Trans. Amer. Climatological Assn., 1898, 14, pp. 276-320.
4. Vagedes: Ztschr. J. Hyg. u. Infektionskh., 1898, 28, pp. 276-320.
5. Lartigau, August Jerome: Abstr. presentation, Jour. Med. Res., 1901, 6-N.S.I. pp. 156-162.
6. Veszpremi, D.: Centralbl. Bakt. Parasitenk., 1, abt. Orig., 1903, 33, pp. 176-184 and 255-259.
7. Dorset, M.: U. S. Dept. of Agric., 21st Annual Rep. of the Bureau of Animal Industry, 1904, pp. 159-169.
8. Fraenkel, C., and Baumann, E.: Ztschr. f. Hyg., 1906, 54, pp. 246-261 and 55, pp. 327-330.
9. Marmorek, Alexander: Berl. klin. Wchnschr., 1906, 43, pp. 328-329.

the anatomical lesions, and only in a very insignificant manner considered the duration of life as a criterion of the infectious power of tubercle bacilli. Rodet and Delanoe[10], as late as 1908, apparently ignoring earlier literature, studied twenty-six cultures from sputum and believed they saw a relation between the virulence of the bacilli and the rapidity of the case in man. Meyer and Lewis,[11] in 1913, in the few cultures of extreme types that they studied, could see no such relation. Gilbert and Gregg,[12] in an excellent investigation, reported before the National Association of Immunologists in 1915, demonstrated that thirteen freshly isolated cultures of tubercle bacilli, mostly from sputum, were capable of infecting guinea-pigs in minimum lethal numbers from 10 to 120 bacilli, the organisms having been counted by the Barber method. The authors state that "In spite of the small numbers of cultures as yet studied, it is certainly safe to assert that great differences in virulence occur in virulent cultures obtained from various cases."

The investigations to be reported on in this paper were not carried on with a view of determining the smallest number of individual bacilli necessary for causing an infection with a view to producing immunity with them, as was the case in Webb, Gilbert and Gregg's work, but rather to determine the ranges in virulence of the bacilli as found in the sputum, with a view to practical hygienic and sanitary significance. For this reason the elaborate and time-consuming Barber method was not used, but it was deemed satisfactory to weigh the bacilli, grind them carefully, dilute them, and count the bacilli by staining them after mixture with blood of known corpuscle content. The number of bacilli thus found per milligram of moist culture were about 5 to 6 billion, so that the lowest dilution used, 0.000,000,01 milligram, contained approximately 50 to 60 bacilli in lumps of no more than 2 to 10 bacilli.

10. Rodet, A., and Delanoe, P.: Compt. rend. de l'Acad. des Sc., 1908, 147, pp. 500-502.
11. Meyer, Karl F., and Lewis, Paul A.: Trans. Natl. Assn. Study and Prev. of Tuberc., 1913, 9, p. 332.
12. Gilbert, Geo. Burton, and Gregg, Harold: Med. Rec., 1915, 88, p. 208, and complete manuscript of this paper kindly sent to author.

A total of eighty-two cultures, directly isolated from the sputum by Petroff's method, were thus examined, and all but two of these produced systemic tuberculosis in the guinea-pig, after subcutaneous injection of 0.000,001 milligram. Of the two negative cultures, one was entirely negative, not even producing systemic tuberculosis in the guinea-pig in 1 mg. dose, and the other only produced a slight tuberculosis in 0.001 mg. amounts. Of the eighty cultures that produced a systemic tuberculosis in 0.000,001 mg., eleven were not examined below this amount, sixty-two produced a systemic tuberculosis in 0.000,000.01 mg. amounts within two months, while seven were negative in this amount. Of the eighty-two cultures examined, eighty were definitely of the human variety, one was intermediate, and the other appeared to be definitely bovine (both of these were virulent in 0.000,000,01 mg. amounts).

The cultures were isolated from 57 far advanced (National Association classification), 18 moderately advanced, and 7 incipient cases. Of the 57 far advanced cases, 30 presented severe constitutional symptoms and 10 of these died in the sanitarium within a year, 10 presented moderate constitutional symptoms, 1 dying within a year, and 17 slight or no constitutional symptoms. Of the 18 moderately advanced cases, 2 presented severe (1 of these dying within a year), 5 moderate, and 11 slight or no constitutional symptoms. All 7 incipient cases presented only slight or no constitutional symptoms. As far as could be observed there seemed to be no relation between the severity of the disease in man and the virulence of the tubercle bacillus for the guinea-pig. There was just as little relation between the anatomical involvement in man and the virulence for the guinea-pigs.

DISCUSSION

These investigations have revealed that in the majority of the cases, the tubercle bacilli that can be isolated on artificial media from the sputum of open cases of pulmonary tuberculosis are virulent enough to produce systemic tuberculosis in guinea-pigs in doses as small as 0.000,001 mg., and that the range

of variation of virulence, as was also pointed out by Gilbert and Gregg, was very small; the latter authors found it to lie between 10 and 120 bacilli. If the virulence of the bacilli as cultivated on artificial media is a direct expression of the virulence as they occur in the sputum, there is only one conclusion to be drawn from the above findings as viewed from a practical standpoint, and that is, that the tubercle bacilli discharged by droplet or by expectoration (when still uninfluenced by drying and light) from open cases of pulmonary tuberculosis are a danger to mankind on direct transmission at least. In applying these findings to mankind, there was found in the literature only one reference which would indicate the relation between the number of bacilli of the same culture necessary to infect a guinea-pig and infect man. These observations were made by Webb and Gilbert,[13] in 1914, who found that a culture of human tubercle bacilli sufficiently virulent to infect a guinea-pig when 10 bacilli were used was also capable of infecting a child in approximately the same dose. It seems justified, therefore, to conclude that the tubercle bacilli found in the sputum of open cases of pulmonary tuberculosis (provided those capable of artificial cultivation are a true index of those existing in the native sputum, and all evidence points in this direction) vary only slightly in virulence for guinea-pigs, and are for practical purposes nearly all pathogenic, that is, in 97 per cent. of the cases they will infect a child, as deduced from Webb and Gilbert's observations, in a dose of less, at least, than one millionth of a milligram.

Dec. 10, 1917.

THE ORIGIN, FATE AND SIGNIFICANCE OF OSTEOCLASTS

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Kölliker was the first to urge that the multinucleate giant cells associated with bone development and resorption are the agents of bone destruction. For

13. Webb, Gerald B., and Gilbert, George Burton: Jour. Am. Med. Assn., 1914, 63, pp. 1098-1104.

this reason these polykaryocytes have been termed 'osteoclasts.'

Views as to the origin, fate, and significance of the osteoclasts are not in accord, many accounts dealing confusedly with multinucleate cells of normal and pathological origins. The following study has been made on developing membrane bones of pig and human embryos. A favorable site is found about the walls of the dental alveoli where active bone resorption is preparing for the accommodation of the rapidly growing teeth. Here osteoclasts appear in large numbers.

In regions where bone is actively forming, the osteoblasts are columnar and distinct with basophilic cytoplasm. During development, the cytoplasm diminishes in amount, and in older regions the still basophilic osteoblasts flatten out and form syncytial masses which become transformed into acidophilic osteoclasts. There were found all transitional stages between these osteoblastic syncytia with basophilic cytoplasm, staining blue with hematoxylin, and typical acidophilic osteoclasts staining red with eosin. Furthermore, osteoclasts were seen frequently continuous at either end with basophilic osteoblasts and particularly with osteoblastic syncytia.

According to these observations, therefore, the oseteoclasts arise from depleted osteoblasts which have first formed a syncytium before being transformed into acidophilic osteoclasts. Nuclear division by mitosis or amitosis has never been observed, although mitoses were not uncommon in the nearby germinative layer of the epidermis. As bone resorption continues, new osteoblasts come into relation with the osteoclasts and are incorporated into them, so that, in general, the larger an osteoclast, the more numerous its nuclei and the more extensive its probable bone-resorptive history.

But the osteoblasts, as such, are not the only source from which the nuclei of the osteoclasts are recruited. Bone cells, embedded in the matrix, are laid bare by the resorptive processes and are ingested by the osteoclasts following in the wake. All intermediate conditions may be found between the initial and final stages of inclusion. Furthermore, bone cells are surrounded normally by a capsule, which resists the action of

strong hydrochloric acid. Encapsulated and distinctly stellate cells, which resemble bone cells, may occasionally be found embedded in the osteoclastic cytoplasm. Such cells are interpreted as bone cells whose capsules are still resistant to cytoplasmic digestion. From the relative infrequency with which persistent capsules are seen, it is probable that the enclosed bone cells are eventually liberated. Ingested bone cells must contribute in substantial numbers to the formation of osteoclasts.

Hence it appears that the degree of multinuclearity is an index of the number of osteoblasts and bone cells entering into the composition of the osteoclasts.

Regarding the fate of the osteoclasts, Kölliker's view that these cells are resolved again into osteoblasts, which may act once more as bone formers, seems improbable. My preparations show nothing in favor of such a cycle, whereas pictures of degeneration in various degrees are abundant; pyknotic and shrunken nuclei, vacuolated and palely staining cytoplasm occur commonly in the older osteoclasts. Neither have I seen convincing stages of a fragmentation into reticular cells of the marrow, as Jackson and Maximow describe. The entire picture, from the early formation by the fusion of depleted osteoblasts, seems rather to depict a progressive degeneration, culminating in death and removal.

Large osteoclasts have been observed rarely in the blood vessels of the bone marrow. That such gain admittance, and do not form *in situ,* is supported by their usual degenerate appearance.

There is no direct evidence as to how bone matrix (inorganic and organic) is resorbed. One may assume that it is essentially a process of decalcification and digestion through the agency of any acid, and, perhaps, an enzyme. The relation of osteoclasts to these changes can only be inferred.

The circumstantial evidence in favor of a resorptive activity by the osteoclast depends on the following relations: (1) osteoclasts appear at the onset of resorption and disappear at its cessation; (2) they are usually closely applied to bone, even following the contour of

irregularly eroded spicules; (3) the frequently occupy Howship's lacunae; (4) a brush border sometimes occurs along the edge next the bone.

The facts tending to discredit the causal relation of osteoclasts to bone dissolution include the following: (1) osteoclasts are notably scarce during the resorption of calcified cartilage; (2) Howship's lacunae frequently lack them—this may constitute a distinct method, "lacunar resorption without osteoclasts" (Kaufmann); (3) it is possible that instead of osteoclasts hollowing out lacunae, the lacunae result from a more rapid independent erosion, perhaps of softer areas, and these, on the contrary, merely trap the giant cells; (4) a 'smooth resorption' of bone in the absence of either lacunae or osteoclasts is known (Busch); in osteomalacia resorption proceeds in the absence of osteoclasts, although typical lacunae may occur; (6) absorption independent of specific cells is a common process in the body; (7) the evidence presented in this paper points toward the osteoclasts as progressively degenerating cells; it is difficult to believe that bone-forming cells, when degenerating, become bone destroyers.

SUMMARY

1. Osteoclasts arise from syncytia of depleted osteoblasts whose cytoplasm becomes acidophilic.

2. The numerous nuclei of large osteoclasts are derived (*a*) from the constituent osteoblasts, and (*b*) from bone cells which are ingested as the bone matrix is resorbed.

3. Eventually the osteoclasts disappear by extreme degeneration.

4. Only indirect evidence points to the osteoclasts as the active agents of bone resorption; in certain cases resorption surely occurs in their absence. Osteoclasts can be interpreted satisfactorily as degenerating, fused osteoblasts.

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BOVINE TUBERCULOSIS

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It was not until I had accepted the kind invitation of your secretary to present a paper on bovine tuberculosis that I realized the difficult task I had undertaken. The subject is so large and so full of economic, sanitary and public interest that one cannot hope to circumscribe it in a single address. It seemed, however, that it would be more helpful to deal with it as a unit rather than to dwell on any particular research and to place in as bold relief as possible some of the technical questions that have arisen in connection with this most serious of cattle diseases.

Historically, bovine tuberculosis is among the oldest of the known cattle diseases, but, like other specific maladies, its nature was not understood. As early as 1370 it was forbidden in Munich to have on sale the flesh of animals affected with tuberculosis. In 1702 Florinus emphasized the then widespread opinion that it was identical with syphilis. In 1783, the Berlin Board of Health rejected the theory of any relationship between bovine tuberculosis and syphilis, and declared the flesh of animals affected with tuberculosis to be fit for food.

In 1816, Tscheulin recognized three degrees of bovine tuberculosis in connection with infected meat: (1) animals in which the tubercles were to be removed and the flesh used; (2) those in which the diseased

parts were to be destroyed and the meat sold at a low price; and (3) those that were so badly diseased that the entire carcass should be condemned.

The early study of tuberculous lesions gave rise to a number of theories concerning their nature. Thus, Virchow, Schuppel and others declared that the tubercles in cattle were lympho-sarcomas. Leisering considered them as simply sarcoma. Spinola and Haubner maintained that human and bovine tuberculosis were identical. Later Von Behring advanced the opinion that most human tuberculosis was contracted from infected milk.

Tuberculosis has been the object of a succession of important researches and investigations since Villeman demonstrated its infectious nature in 1865. Following this announcement attention was centered on its etiology until Koch's discovery in 1882. Then special effort was made to determine the nature of the reaction of the tissues to the invading organisms which differentiated its lesions from the other infectious granulomas of earlier writers. The discovery of tuberculin was followed by a large amount of experimentation relative to its therapeutic and diagnostic value. The differentiation of the human and bovine varieties of tubercle bacteria called forth many researches that resulted in greatly modifying the sanitary aspect of this disease. These special studies were accompanied by vigorous efforts to eradicate it.

The nature and distribution of the lesions in bovine tuberculosis are of much interest. The fact that it is usually a local disease in the beginning and often remains as such for years, without endangering other animals, has been difficult for sanitarians to appreciate. It is in the varied location of the tubercles within the body, the manner of their development and the irregularity in the elimination of tubercle bacteria that we find an explanation for the different methods of control. I desire, therefore, to consider, in addition to the tissue changes, certain methods for its control and the problems that have presented themselves in connection with their development. The history of certain of these methods illustrates

as clearly as any other phase of applied science the difficulties and disappointments that follow efforts to apply knowledge before it has been acquired. Human medicine should profit from the hasty conclusions that were drawn and the applications that were made of a few facts regarding tuberculosis, tubercle bacteria and tuberculin before the nature of the disease was understood and the limitations of tuberculin recorded.

The structure of the tubercle is essentially the same in cattle as in other species. In the beginning the reaction of the tissues to the invading organisms consists of a few cells surrounding the specific bacteria. They are early encased by a zone of epithelioid and giant cells, which in turn is surrounded by a reactionary outer layer composed largely of lymphoid tissue. As the tubercle is nonvascular, the central portion undergoes necrosis. With the growth of the lesion the central necrotic area becomes correspondingly large. This structure is illustrated more clearly in the early stages of the avian tubercle. In cattle there is a strong tendency for the dead tissue to become infiltrated with lime salts. In certain species, especially the experimental animals and frequently in swine, the lesions have a tendency to become more diffuse, infiltrating the interstitial tissue and gradually encroaching on the parenchyma.

The location of the primary tubercles depends on the channel of infection. If the specific organisms are lodged in the oral cavity or pharynx they may pass through the mucosa to be taken to some of the lymphatic glands about the head; if they are taken directly through the respiratory passages into the lungs they either develop tubercles in the lung tissue proper or they are carried through the lymphatic system to the lymph glands, draining the lungs where the lesions first appear. If the bacteria are first lodged in the intestinal mucosa, primary tuberculous ulcers may develop or, as usually happens, they pass into the mesenteric lymphatics or the portal vein. In this case the primary lesions may occur in the mesenteric glands or liver. However, the bacteria may pass

through the lymphatics and thoracic duct into the general circulation, from which they may be lodged or filtered out in any organ or tissue of the body.

The evidence at hand indicates that in a large majority of cases the primary lesions are located in one of the following organs: in the lungs or in the lymphatic glands draining them; in the lymphatic glands about the head; in the intestines or mesenteric glands; in the portal glands or liver substance itself, and in the generative organs and udder. It occasionally happens that the primary lesions occur in the bones, on the pleura, peritoneum, meninges, synovial membranes or skin, while the organs usually attacked remain free from lesions. One of the distinctive features of bovine tuberculosis is the frequency with which the serous membranes, especially the pleura, are affected. The lesions consist of nodules, varying in size from that of a millet seed to a large pea, sprinkled more or less thickly on one or both of the visceral or parietal surfaces. These form the "pearl disease" of the German writers, and the "grape disease" of the English authors. If these tubercles become confluent, large masses of necrotic, usually calcified tissue, surrounded by a thin wall of fibrous tissue, are observed. Joest and Marjanen found that in serous tuberculosis in cattle there are produced nonspecific inflammatory new formations which become infected with tubercle bacteria and result in the formation of the "pearl" nodules. This form of tuberculosis is very common, and frequently when the pleura are involved the lung tissue remains apparently normal.

Dr. W. L. Williams has recently presented a very instructive paper on the frequency with which the generative organs of both sexes are affected with this disease. He has called attention to its significance in the production of sterility. The udder becomes the seat of tuberculous deposits in a small percentage of cases. It is affected more often in generalized tuberculosis, although cases of primary lesions in this gland have been found. McFadyean finds from 1 to 2 per cent. of udder tuberculosis; Poels, 9 per cent.;

Vallée and Villejean, from 5.3 to 6.5 per cent.; and Bergman, 3.5 per cent.

Advanced cases of bovine tuberculosis are instructive in showing the succession of "crops" of tubercles. As many as five generations have been observed. These are rarely if ever found except in animals that are about to die. A large part of the study of tuberculosis has been made on animals slaughtered after the tuberculin test and when the disease process is usually in its early stages. This has failed to give the proper conception of the extent to which the organs of the body may be destroyed and the animal still live. When the specific organisms have spread from the seat of infection or the primary lesion through the blood stream, sprinkling other organs with the infecting bacteria, the disease has become generalized. Formerly it was so considered where the lesions existed in both the large cavities (abdominal and thoracic). It is possible, however, for it to be generalized when the tubercles are found in the organs of a single cavity. The secondary seeding with the bacteria that have escaped from the primary focus through the circulation may be limited to the cavity containing the primary lesion.

Klencke called attention to the sanitary significance of bovine tuberculosis in 1846. That year he published a work in which he maintained that there was a positive connection between the milk of tuberculous cows and the frequent development of scrofula in bottle-fed children. After Villemin's experiments. Gerlach showed that tuberculosis could be produced in animals by feeding them the fresh milk of tuberculous cows. The belief that human and bovine tubercle bacteria were identical and Von Behring's views of human infection from milk added much to the importance of this phase of the disease. The discovery of tuberculin and the fact that it gave a reaction when injected into tuberculous, but apparently healthy, cattle added still greater significance to this subject. Later the differentiation of the human and bovine varieties of tubercle bacteria pointed out very clearly that bovine tuberculosis was not as important

a factor in the production of this disease in the human family as it had been thought. The researches on this phase of the subject have been numerous. They have shown that in adults there is but little if any infection from the bovine type of tubercle bacteria, but that young children are susceptible and frequently become infected with it.

Efforts to control bovine tuberculosis began in this country with the discovery of tuberculin, and in the beginning it was prosecuted as a sanitary measure only. The method introduced in Massachusetts and New York in the early nineties was the first official procedure to eradicate this disease. It was initiated when health officials believed that tuberculosis in man was contracted from cattle and with the implied conviction that all reacting animals were immediately dangerous. The system required that the state or federal government should pay an indemnity for the animals slaughtered. This expenditure was justified on the ground of public safety and equity to the owners. It was found, however, that tuberculosis was much more prevalent than it was supposed, and that to test all the dairy cattle, kill all the reactors and compensate the owners would not only cost more than the legislatures would appropriate, but also that it would be disastrous to our breeding and dairy herds. Further, it was learned with much embarrassment to the advocates of the method that, while it often succeeded, many herds which were treated by it subsequently were infected as extensively as before. The failure of this method to insure clean herds brought about numerous modifications of the system. The method assumed that the diagnosis was based on an exact science.

In Denmark and other European countries more conservative measures were employed. Among these the one introduced by Professor Bang of Copenhagen and which bears his name has been most successful where it has been carried out. It requires the testing of all cattle in a herd with tuberculin; killing for food, under inspection, all animals that show, on a physical examination, any evidence of disease; sep-

arating the reactors from the nonreactors, and raising the calves on pasteurized milk or that from sound nurse cows. When a reactor shows physical signs of disease it is removed and slaughtered. The reactors gradually disappear and their places are filled with healthy offspring. Meantime the owner has learned something of the nature of tuberculosis and is able to keep his herd from reinfection.

In Denmark, the Bang method has been very successful, because the people allowed the use of the milk of the apparently sound but infected and reacting cows. This enabled the owner to purify his herd without financial ruin. All creameries pasteurized the separated milk before it was returned for feeding purposes. In 1908 the health authorities of Copenhagen claimed the lowest death rate among children of any city of its size. In the United States this method has not worked generally, because people would not allow the sale of milk from cows that had reacted to tuberculin, notwithstanding that all physical cases of the disease had been removed and the milk was much safer than before. This made it financially impossible for our dairymen to apply the method, except in cases of very valuable breeding animals. When the extent of bovine tuberculosis was recognized, the necessity for its control, from an economic point of view, was apparent. Already many breeders had lost their herds in complying with the official method, and others had purchased high-priced animals, on the tuberculin test, and later had found them to be affected. Numerous producers of certified milk had had similar experiences. It was clear, therefore, that if the control of this disease was to succeed, investigations must be made to ascertain the cause for the occasional failures in diagnosis. It was also necessary to determine what principle should be observed in detecting spreaders. This pointed to further bacteriological examinations of the milk and excreta and determination of the limitations of tuberculin. It required no prophet to foretell the victory of bovine tuberculosis in our breeding herds, unless the errors that appeared in the method of con-

trol, insisted on by sanitarians, could be corrected. The purchaser of cattle knew that a test following the one made at the time of purchase would give a greater or less number of reactors. The medical profession as represented in the health departments explained these seeming discrepancies as the result of fraud. It was known to some, however, that this was not always the case, for in certain experimental work the results were the same.

The first subject which we took up was a study of the elimination of tubercle bacteria from reacting cows. A large number of examinations of this kind had been reported which indicated that the milk of practically all reactors was infectious. The location of the lesions in the cows from which the milk was taken was usually omitted by the authors. This made it impossible to determine whether or not the infected milk came from animals with tuberculous udders.

In 1907 we made examinations to ascertain how frequently tubercle bacteria appeared (1) in the mixed milk of herds containing reacting animals, and (2) the extent to which reacting cows with sound udders were eliminating the organisms. The results of this preliminary study showed that of the forty-nine samples of mixed milk, acid-fast bacteria resembling those of tuberculosis were found microscopically in one specimen, and guinea pigs inoculated with the mixed milk from two herds which contained advanced cases of tuberculosis developed the disease. The physical cases were removed from these herds, and subsequent inoculations gave negative results. Of the eighty-seven examinations of the milk from individual cows, tubercle bacteria were not found either microscopically or by guinea-pig inoculations, except from two cases, and they were cows with affected udders.

These preliminary investigations were followed by a very thorough study by Peterson on the elimination of bacteria in the milk and excreta of reacting cows which exhibited no evidence of lesions. The examinations were repeated frequently over a period of several months to ascertain whether in such animals the specific organisms were eliminated intermittently.

The milk of seventeen reacting cows was examined. The milk was examined microscopically and guinea-pigs were inoculated. Peterson drew the following conclusions from this study, namely:

"The tuberculous cattle examined that were apparently sound, but which reacted to the tuberculin test, did not eliminate sufficient tubercle bacilli to cause the death of experimental animals when injected with their milk or excreta or for the same to be demonstrated microscopically.

"The animals that showed marked physical signs of tuberculosis eliminated tubercle bacilli in sufficient numbers to be detected microscopically or by animal inoculation in a large percentage of samples of milk and excreta taken at regular intervals. Single examinations of the milk or feces might have negative results."

A significant fact brought out in this work was that while the milk of these animals did not contain the organisms so long as lesions did not appear in the udder, and there were no evidences of intestinal or lung infections, when the cows developed pulmonary lesions tubercle bacteria appeared in their sputum, and the feces contained the organisms in sufficient number to kill guinea-pigs inoculated with it. We have found very small tubercles discharging into the bronchioles and also in the trachea. This shows the possibility of tubercle bacteria gaining access to the milk of cows suffering with pulmonary or intestinal tuberculosis and whose udders are not infected.

Three experiments were made by injecting tubercle bacteria intravenously into milch cows and examining their milk at short intervals for the organisms. These gave invariably negative results, although the animals developed miliary tuberculosis, especially of the lungs, from which they died. Sections of the udder in these cases failed to reveal the presence of tubercles. The lungs, however, contained enormous numbers of them. While these examinations were few in number, they indicate that tubercle bacteria which may be temporarily in the circulation are not readily eliminated

through the milk ducts. It is possible that they may develop lesions in the udder from which the organisms may escape into the milk. These examinations threw much light on the conditions under which tubercle bacteria may appear in the milk. As fecal contamination of milk frequently happens there is a possibility of its becoming infected from reacting cows with sound udders.

Many years ago Ravenal pointed out the feasibility of diagnosing tuberculosis in cases of pulmonary affection by means of sputum examinations. Our examinations have shown that occasionally animals which have passed both the physical and the tuberculin test eliminate the specific organisms with their sputum. In 1912 Scharr and Opalka emphasized the importance of securing mucus from the lower part of the trachea and bronchi for the purpose of diagnosis and also for finding spreaders. Their method consisted in inserting a sharp trachea tube between two of the cartilaginous rings, through which a long wire was passed with an eye armed with a small piece of sterile gauze. With the mucus thus collected microscopic examinations were made and guinea-pigs inoculated. Before this, Hazenkamp suggested the use of a "Lungenschleimfänger," or a metal cup, attached to a wire, which was inserted into the esophagus and withdrawn, thereby scraping the mucus from the walls of the esophagus and collecting it in the cup. This could be subjected to a bacteriologic examination. By means of the sputum cup Udall and Birch have been able to find spreaders among cattle that have passed the tuberculin test, as well as among those that had not been tested. They found, among tuberculous cattle which they examined, that one cow in five was carrying tubercle bacteria in the esophagus.

A second and equally important problem was to ascertain the reliability of tuberculin. The earlier method of control assumed that it would give a reaction in all infected animals. The practice was to test the herd, destroy the reactors, disinfect the premises and go away with the conviction that the herd

was freed from this infection. Boards of health and sanitarians placed great importance on this procedure. In a large number of herds, especially small ones containing recently infected animals, the result was most satisfactory, but in others, in which the disease had existed for some time, this was not the case. The number of tuberculous animals which did not react in such herds varied within quite wide limits. The tentative explanation was that some error had been made, but its occurrence in experimental animals indicated other reasons. It was not until careful studies were made into the theories for the cause of the reaction that an explanation for these failures could be found.

A practical illustration of the nonreaction to tuberculin in infected animals is found in this experience. In the spring of 1904 I tested a herd of 491 animals, of which ninety-six cows did not react. All of the others responded and some of them were physical cases. The nonreactors were placed by themselves in a practically new barn, and three months later and every six months thereafter for more than three years the sound herd was tested. Those that responded were promptly removed and the stable thoroughly disinfected with 5 per cent. carbolic acid after each test. The results of the consecutive tests of the nonreacting animals are exceedingly instructive. They are as follows:

Results of the Study by Consecutive Tests of the Nonreaction to Tuberculosis in Infected Animals

Month and Year	Number Tested	Number Reacted	Number Nonreactors	Percentage that Reacted
April, 1904....	491	395	96	81.5
July 1904....	96	31	65	32.2
Jan. 1905....	65	8	57	12.3
July	57	15	42	26.3
Jan. 1906....	42	15	27	35.7
July	27	3	24	11.1
Jan. 1907....	24	2	22	8.3
July	22	1	21	4.5
Jan. 1908....	21	1	20	4.7
Aug.	20	1	19	5.0

During this time these animals were kept by themselves. There was no opportunity for outside infection after they were removed from the main herd.

Several of the reactors were examined postmortem. The lesions were slight in extent, but of long standing, and were surrounded by a wall of fibrous tissue. Recent tubercles were invariably found budding off from the encapsulated ones or elsewhere in the body.

The failure of tuberculin in tests of this kind led to the careful consideration of two factors: (1) the cause of the reaction, and (2) the detection and interpretation of the response of the tissues to this agent.

Many theories have been advanced to explain the tuberculin reaction, but the one that seems most likely to be correct is that of the hypersensitization of the tissues by the tubercle bacteria. This theory was first suggested by von Pirquet and Richet, who noticed the resemblance between the tuberculin reaction and protein hypersensitiveness or anaphylaxis. Later, Lowenstein and Rappaport interpreted the tuberculin reaction as evidence of hypersensitiveness. Wolff-Eisner, Vaughn and others believe the reaction to be due to an antibody, lysin, or ferment given off by the tissues that already have been stimulated by tubercle organisms. The theory briefly stated is this: Consequent on the stimulation of the body tissues by tubercle bacteria, the animal tissues elaborate specific substances known as lysins or ferments. These bodies attack and rapidly disintegrate tubercle bacteria protein that subsequently may gain entrance into the body. The endotoxins thus set free (the poison group of atoms of the protein molecule, according to Vaughn) act as poisons when the cells of the body are in a hypersensitive state. In normal individuals a very small amount, if any, of the specific lysin is present. For this reason the protein of the tubercle bacterium present in tuberculin is not attacked, and consequently no reaction takes place when it is injected into a healthy animal; but when injected into an infected animal it is acted on by the lysin, which splits it up, thereby enabling at least some part of it to act on the heat centers of the nervous system and cause a rise of temperature. This hypothesis explains why it is that in certain animals a slight or suspicious rise of temperature may follow the injection of tuber-

culin in a tuberculous animal. If the activities of the tubercle bacteria have ceased, at least temporarily, the antibody or lysin may still be present in quantities sufficient to cause a disturbance in the temperature, but not enough to cause a decided rise. The same condition may be present in the very beginning of the disease. Eber's theory as modified by Smith suggests that the antibodies may be closely associated with the lesions. This method likewise explains the phenomena.

If this theory is correct the reaction depends on certain actions in the infected individual between the tissue products or antibodies and the tuberculin. In cases of active or progressive tuberculosis the substances essential for a reaction are present, and in such cases it practically always occurs. Further, the strains of tubercle bacteria may differ in their virulence and the resistance of the animals may vary. It is not possible to know whether, under these modifications, a reaction will or will not take place. The best that can be done at present is to gather from experience the results obtained under fairly well-defined conditions when the examination of animals that failed to react showed the presence of tuberculous lesions.

A careful inquiry into the cases in which tuberculin has failed to produce a reaction in tuberculous animals has revealed several possible defects in the preparation of tuberculin and a few conditions in the infected or diseased animal under which a reaction does not take place. These may be summarized as follows:

1. All strains of tubercle bacteria do not make an efficient tuberculin. When it is made from some organisms, a reaction does not follow its use.

2. When the cultures of tubercle bacteria to be used in making tuberculin are not properly grown, that is, when there is too much liquid for the surface area, it does not contain an adequate quantity of the specific protein to enable it to cause a reaction.

3. When, in the application of tuberculin, the observation of the tested animal is inadequate to detect its effect the reaction is missed.

4. When the interpretation of the manifestations following the use of tuberculin is not made in accordance with the laws governing the reaction between it and the products of tuberculous lesions in the living animal.

5. When tuberculin is applied in the period of incubation.

6. When the tuberculous lesions are arrested, healed, encapsulated or very extensive, tuberculin often fails to indicate the presence of the disease.

7. When tuberculin is administered repeatedly, at short intervals, a reaction is liable not to follow after one or more injections.

It is obvious that failures due to the improper preparation of tuberculin, inability to detect a reaction or to correctly interpret it, should not be recorded against its efficiency. It can be appreciated, however, that neglect to guard against these might result in serious consequences. In fact, many herds have been ruined by such neglect, and tuberculin as a diagnostic agent has been condemned by practical breeders whose co-operation is especially needed. The great accuracy of tuberculin that has been pointed out by several writers pertains to the positive reactions only. Thus, it is stated in a farmer's bulletin on this test that out of 24,784 reacting cattle slaughtered 98.39 per cent. showed the lesions. There is no record of the postmortems of those that did not react. I believe that an unquestionable reaction is a sure indication of the presence of tuberculosis.

The detection of a tuberculin reaction from the rise of temperature is not always easy, and the organic manifestations described by Nocard are occasionally overlooked. Formerly a rise of temperature of at least 2 F. above the maximum preinjection temperature was considered necessary to condemn an animal. Later a rise of 1.5 F. was accepted officially as evidence of infection. In an experiment station bulletin of much excellence this statement is made: "Usually in the postive reactions the maximum temperature on the day following the injection is from 3 to 5 F. above the normal temperature." The thermal reaction, con-

sisting of a gradual rise, a festidium and a gradual decline, has been designated the tuberculin curve. When it is high and regular it is a very sure indication of tuberculosis. When, however, the elevation is not greater than may occur within physiological limits, the curve must be studied carefully and the decision as to whether or not there is a reaction determined on the case in its entirety. Other evidence, such as chill, dullness or general malaise, may accompany these low thermal reactions. Many of these cases cannot be accurately interpreted and the decision must be delayed. Such indeterminable cases should either be slaughtered for food or kept under careful observation for subsequent examinations. Some years since I had the opportunity of making a postmortem on seventeen animals that gave postinjection temperature curves in which the maximum temperature was less than 103.5 F. and less than 1 F. above the preinjection record. All of these had been passed, because the elevation was less than the official requirements for condemning the animals. Five of the seventeen were adult cows and twelve were between 6 and 18 months of age. All of the five cows were tuberculous and six of the younger animals showed unquestioned lesions of tuberculosis, and in one of them the lesions were generalized and the carcass was condemned. In the remaining six tubercles were not found. Undoubtedly, many infected animals have been passed because the rise of temperature was not sufficient to condemn under existing regulations. These doubtful reactions are important. They must be dealt with wisely if the reputation of tuberculin is to be maintained and justice meted out to the animal and its owner.

Another cause for error has been the very early and the late reactions. Thousands of tests have shown that temperature elevation following tuberculin usually begins in from six to ten hours, more often about the eighth, after injection; that it remains high for from one to six hours or more, when it returns to the normal. Occasionally, however, the reaction begins much earlier and its duration is shorter and the temperature subsides to the normal by the tenth or twelfth

hour. In other cases the rise of temperature does not begin until much later, eighteen to thirty-six hours after injection. Because of the labor involved tuberculin tests do not extend usually over a period of more than twenty-four to twenty-six hours, including the preinjection temperatures. By this method the exceptional cases of early and late response are missed and the infected animals are passed.

The tuberculin is usually applied by subcutaneous injection. Within recent years a number of other ways have been devised for its administration. Among these the ophthalmic and intradermal methods have received most attention. In several states the intradermal test is recognized officially. Here the tuberculin is injected with a short needle into the skin itself, usually at the root of the tail or into the palpebral glands. The reaction consists of a swelling which can be detected in from eighteen to seventy-two hours after the injection. Haring, in California, has reported most excellent results from this method, and he has also found that certain animals that failed to give a reaction to the subcutaneous injection did respond to the intradermal. The ophthalmic method is favored by some, but generally it is not received with favor.

There is much discussion at the present time as to which method of administering tuberculin has a claim for the greatest accuracy. In my experience the subcutaneous injection has been more satisfactory. I do not believe, however, that it is possible to decide which method is most efficient until we understand more thoroughly the reason for the reaction.

It is not revealed which organs or tissues are most highly sensitized in cases of tuberculosis. The relation between the location of the tubercles or their number and the degree of sensitization has not been determined. There is some evidence that the reaction is closely associated with the lesions themselves. It has been reported that if the tubercles are removed and the animal tested subsequently negative results follow.

During the last few years we have made several

experiments in this line to ascertain, if possible, the extent to which reaction was determined by the lesions themselves. For this purpose calves were used. They were inoculated carefully in one of the external inguinal glands. After the glands became enlarged, as a result of tuberculous infection, they were removed and the animals tested. In the few cases in which metastasis had not taken place prior to the removal of the tuberculous glands no reaction was obtained. The check calves from which the glands were not removed gave an unquestioned response to the tuberculin. These experiments will be published after a further test has been made. Much more research work is necessary before the question as to the seat of the reaction can be answered and before the relative efficiency of the different methods of applying tuberculin can be determined. The agglutination test has been reported with some favor in human tuberculosis. It has not proven successful in my hands for detecting the disease in cattle.

The diagnosis of bovine tuberculosis is a much more difficult task than is usually believed. It is true that a majority of cases respond to tuberculin, but a certain number do not. It is the refractory cases, which are often spreaders, that have caused so much difficulty in the eradication of the disease. It is unfortunate that professional men have not given more consideration to these fundamental principles in the effect of tuberculin. Legislators have been influenced by the assurances of its practical infallibility, so that laws have been enacted centered on its use rather than the diagnosis of the disease. These have tended in individual herds to retard rather than advance elimination. We are coming to understand the difficulties and to appreciate the "symptom complex" in diagnosis.

A large amount of work has been done in search of an efficient method to immunize cattle against tuberculosis. The results have shown that some resistance can be developed, but that the production of immunity as a practical means of combatting tuberculosis cannot

be accomplished by any means known at the present time.

I have emphasized the question of diagnosis, especially of the occult cases, for the purpose of bringing out the limitations of tuberculin, an explanation for at least many of its failures and the end to be derived from bacteriologic examinations. This seemed advisable, because errors in detecting the disease in apparently healthy animals have interfered seriously with progress in the eradication of bovine tuberculosis. Many breeders and dairymen have bought animals on the tuberculin test and placed them in healthy herds. At a subsequent test not only the new animals, but also those already in the herd infected by them have reacted. Naturally this has caused doubt as to the efficiency of tuberculin. Unfortunately there has been a tendency for sanitarians, even in the face of such experiences, to insist on the accuracy of tuberculin and to explain the failures on other grounds. The crux of any method for eradicating bovine tuberculosis is the diagnosis of infected animals, that cannot, from the very nature of things, respond to tuberculin. This means that not only shall the tuberculin test be repeated at proper intervals, but also that other examinations shall be made.

The point that must be attained by education and regulation is the prevention of the spread of the infecting organisms. This means that the herd shall be the unit to deal with, and that infected animals shall not be allowed in the channels of trade, except as they are sold for immediate slaughter under inspection or to go into known tuberculous herds where the Bang or other conservative method is being applied. The two points to be emphasized are that healthy herds must be maintained as such and that infected herds shall be purified. Because of the insidious nature and the slow development of tuberculosis it has gradually grown into many herds, and now it must be directed in such a way that it will grow out.

Finally, it is not possible to indicate in the abstract what particular regulations should be specified for the control of this highly parasitic disease. The con-

ditions vary in different herds and the remedy must be adjusted to the individual cases. The natural history of tuberculosis indicates that it can be eliminated but that ordinary eradication cannot be accomplished quickly except by slaughter. The experience with many herds in which the infection existed to a fearful extent has demonstrated that the disease can be eliminated and that with its going out a new and healthy herd can be grown up to take the place of the diseased animals. Never before has the medical profession been called on to formulate methods for eradicating widespread diseases when the infected animals still retain an intrinsic value for food or breeding purposes. While this complicates the problem, it adds interest to it. It brings us face to face with a necessity of applying biologic knowledge to an important human industry. Problems as difficult as the eradication of tuberculosis from our dairy herds have been solved and with patience, education and cooperation the extent of this disease can be reduced to a minimum.

Feb. 6, 1918.

CALCIFICATION AND HEALING OF AN ACUTE DISSECTING ANEURYSM OF THE HEART WITH MARKED DEFORMITY

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(From the Pathological Laboratory, Rush Medical College, Chicago)

During the course of malignant endocarditis, or as it is perhaps better termed, thrombo-ulcerative endocarditis, it occasionally happens that cavities are formed by necrosis in either the valves themselves or in the parietes of the heart or adjacent large arterial trunks and such cavities made larger by the splitting force of blood driven into them by systolic contraction. In this way acute dissecting aneurysms develop in the heart walls or in the roots of either pulmonary artery or aorta. The more frequent location of such lesions about the aortic valves and their

disposition to rupture into the pericardial sac were thoroughly discussed some years ago by Vestberg.[1]

There is, however, practically no mention in medical literature of the arrest of such lesions; aneurysms of of the heart produced in this way usually bring about death by rupture as stated, or death results from the endocarditis and its concomitant metastatic processes while they are still acute or subacute and the small unruptured aneurysms are found by necropsy.

The following description, it is believed, deals with a heart in which from the location of the lime deposits and the alterations of the valves, calcification of thrombi occurred in places about the aortic root in such a manner that the most proper assumption is concerned with not only a former acute thrombo-ulceration endocarditis, but also with cavities hollowed out by both acute or subacute necrosis and by blood forced into them.

W. B., laborer, aged 68, was admitted to the Hospital of the House of Correction to the service of Dr. C. E. Sceleth for treatment for alcoholism. The patient was found to be partly paralyzed on one side and a systolic murmur loudest over the mitral area transmitted to the axilla was heard on examining the chest. He lived only three days.

At the postmortem examination in addition to a place of softening in one cerebral hemisphere and some chronic tuberculosis of the lungs, an unusual disease of the heart was found for which it is hoped the following account may in some measure be adequate.

The left ventricle of the heart is large and alone forms the apex, the right ventricle small. The root of the aorta bulges forward displacing the pulmonary artery slightly to the left. On the front of the left ventricle there are a few small opaque fibrous patches in the epicardium. To the right of the conus of the pulmonary artery and in front of the septal tricuspid leaflet there is a hard mass of lime continued through the wall between the ventricles from the aortic root; it lies partly in the conus arteriosus.

At the level of the free edge of the aortic valve leaflets the orifice is 9 cm. in circumference. There is a thin calcareous plate 2.8 cm. long and 7 cm. wide in and at the

1. Nord. med. Arkiv., 1897, 29, Nos. 26 and 27; also, Hygiea, 1893, 55, p. 121.

attachment of the left cusp (Fig. 1 d). The node of this cusp also contains lime, is 12 mm. long, 6 mm. deep and 2 mm. wide. There are similar patches of lime at the attachment of the posterior cusp, one 8 mm. long and 4 mm. wide, the other 1 cm. long, 0.6 cm. deep and 0.2 cm. wide (Fig. 1 c). Above the attachments of the aortic leaflets in the wall of the aorta there are a few small deposits of lime (Fig. 1 a). There are two openings for the right coronary artery in the aorta, the larger a little to the left of its usual position; otherwise the mouths of these vessels are unchanged (Fig. 1 b).

At the base of the right aortic leaflet where the wall of the aorta joins the membranous portion of the interventricular septum there is extensive deformity (Fig. 2 d and 1 f). Here a "pocket" is formed about 1.6 cm. deep extending

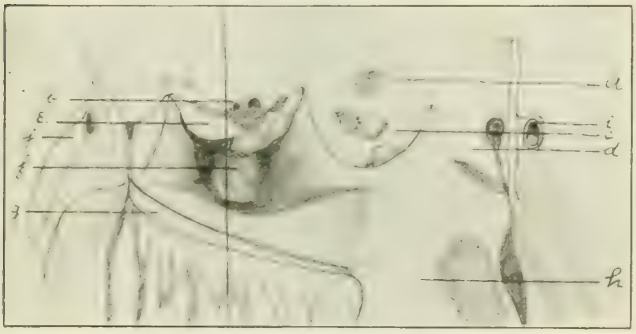


Fig. 1.—The left ventricle, front mitral leaflet and aortic root, the vertical line indicating where the cut was made yielding two surfaces, one of which is shown in Fig. 2; a, patches of line in the aorta; b, accessory opening of the right coronary artery; c, posterior aortic leaflet; d, left aortic leaflet; e, right aortic leaflet; f, bottom of "pocket"; g, lower wall of "pocket"; h, anterior mitral leaflet; i, left coronary artery; j, right coronary artery.

down into the membranous septum, deepest opposite the middle of the right cusp. The lower wall of this "pocket" is formed by a thin fibrous ridge 4 cm. long, which extends from a fibrous triangular region at the right of the anterior mitral leaflet to the middle of the base of the left aortic cusp (Fig. 1 g). This ridge or little shelf is 3 mm. above the muscular septum and with the membranous septum about 1.6 cm. below the free edge of the right aortic cusp. The upper wall of the "pocket" is formed by the right aortic leaflet nearly the entire left half of which is occupied by a

large irregular calcareous plate 2.5 cm. by 1 cm. At the attachment of the cusp it is 5 mm. thick. It extends into the wall of the aorta so that the cusp is rigid (Fig. 1 c). At the bottom of this "pocket" is a large, rough calcified mass 5 by 8 by 7 mm. in its greatest dimensions (Fig 2 d and 1 f). In part it is not covered by endothelium and has a rough nodular yellow surface. The mass is free in front and to the right and left. Above it is continuous with the deposit of lime in the right cusp (see Fig. 2 b and d). Below and

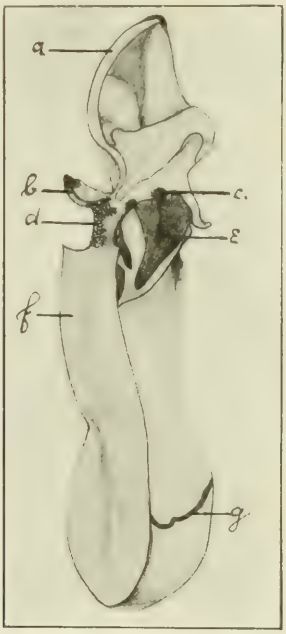


Fig. 2.—The front of the two surfaces made by a single incision (indicated in Fig. 1) through the middle of the right posterior aortic leaflet and parallel with the long axis of the aorta. a, aorta; b, right aortic leaflet, cut through; c, lime in the wall of the right ventricle; d, bottom of "pocket" with "shelf"; e, cavity of right ventricle; f, wall of left ventricle; g, coronary artery.

behind it extends into the membranous septum through which it reaches the lining of the right ventricle at the level of the origin of the large papillary muscle and just at the upper margin of the beginning of the pulmonary conus (Fig. 2 c). Here there is a fibrous lime-infiltrated place,

the lime continuous with that of the mass just described. It reaches the surface here and forms a patch in the right ventricle 6 by 2 mm. (Fig. 2 d and c). The wall of the pulmonary conus is puckered by this calcified scar and its channel narrowed at its beginning to 7.1 cm. circumference. The left half of the front mitral leaflet is bound down by fibrous tissue to the scar.

The orifice of the pulmonary artery in the right ventricle is 7.3 cm. in circumference. Except for the narrowing of the conus and the projection into its lining of the lime deposit already described there is no change in the right ventricle. The pulmonary leaflets are normal. The wall of the right ventricle at the middle of the base of the anterior cusp is 5 mm. thick. At the origin of the large papillary muscle it is 4 mm. thick. In the endothelium of the septum there are a few small thickened gray patches. The circumference of the tricuspid ring is 11 cm. The middle and posterior cusps are unchanged, the anterior cusp adherent as already described. Two cm. above the attachment of the tricuspid leaflets at the level of the right auricular appendages the circumference of the right auricle is 11.5 cm.

The mitral orifice admits four finger-tips snugly. At the apex of the heart in front close to the septum the wall of the left ventricle is 1.8 cm. thick; midway between the apex and mitral orifice 1.9 cm. The mitral leaflets are slightly thickened and opaque and there is a large, thin calcareous patch on the anteror leaflet (Fig. 1 h).

The left auricle is grossly unaltered, the foramen ovale closed. The coronary arteries are tortorous and their walls hard in many places.

Nov. 12, 1917.

EARLY CHORIO-EPITHELIOMA OF THE UTERUS

E. H. WARSZEWSKI

(From the Laboratory of Pathology, Cook County Hospital, Chicago)

In the literature there appear reports of some 340 cases of chorio-epithelioma, the great majority primary in the uterus, tubes or ovaries and following hydatidiform mole, a normal labor or an interrupted pregnancy. A few not associated with pregnancy, are recorded in which the tumor began in the testicle, brain or uterus of children. The neoplasm then is

not at all uncommon. It is believed though, that this case may prove of sufficient interest to warrant a brief report.

Woman, aged 34, entered the Cook County Hospital to the service of Dr. H. M. Stowe, Sept. 28, 1917, complaining of a bloody vaginal discharge, extreme weakness and loss of weight. In March, 1917, she was delivered of her first child. Six weeks after labor, bleeding from the vagina appeared and persisted for two weeks, and then intermittently up to the time of operation. Temporary relief followed a curettement in July, 1917, at another hospital. The bleeding soon recurred, however, and became progressively worse; large clots of blood were frequently passed and the patient became weak and anemic. Following this curettement she developed a high fever which lasted about 7 days and lost about 30 lbs. in weight. She was a markedly emaciated, anemic, middle-aged white woman who did not appear acutely ill. Her temperature was 99.4 F., pulse 116, and respiration 22. Shortly after her entrance, she developed frequent chills and sweats which were accompanied by a variable fever. A profuse bloody vaginal discharge admixed with many firm clots appeared. The vagina and perineum revealed no gross abnormalities. The cervix was slightly lacerated, drawn down and fixed to the left side. Tenderness was absent. The red blood count on entrance was 1,548,000, but later rose to 2,000,000 per c.c.

The uterus was curetted once more and this time the material removed was examined microscopically and a diagnosis of chorio-epithelioma made. In November, 1917, following a panhysterectomy, a high fever, tympanites and abdominal tenderness developed and 12 days after the operation, she died of a general peritonitis.

The uterus removed at operation was enlarged to the size of a three months' pregnancy. The tubes, ovaries and broad ligaments were grossly normal. In the fundus, there was a friable papillomatous purplish-red tumor 3.2-3.5 cm. in diameter. The musculature was invaded by several wide, sharply demarcated tortuous projections of tumor tissue which penetrated the uterine wall and appeared beneath the serous surface as confluent red nodules. The subserous tumor mass had a larger area than the intra-uterine portion. It measured 6.3 by 3.6 cm.

At the necropsy (Dr. J. W. Nuzum) there was found in the abdominal wall a recent low midline laparotomy incision from the lower end of which a thick greenish pus exuded. The peritoneum is opaque, lusterless and fibrin-flaked. The loops of the small bowel are distended with gas, matted

together by fibrinous adhesions and bathed in a chocolate-colored exudate. The capsule of the spleen and the anterior and posterior surfaces of the liver are coated with a thick layer of fibrino-purulent exudate. The uterus, tubes and ovaries are missing. The appendix is retrocecal and firmly bound down by fibrous and fibrinous adhesions. The mesenteric lymph glands are hyperplastic. A marked sero-fibrinous pleuritis is present in both chest cavities. A solitary small tuberculous cavity is found in the apex of the right lung. Caseous and fibrous tuberculous nodules are present in both apices. Several pea-sized tumor masses can be palpated scattered through both lungs. These on section present a cherry red, bleeding soft surface, well marked off from the adjacent lung tissue. In the cortex of the right and left kidney, there is a wedge-shaped red infarct 5 mm. in diameter outside and in cortical substance for 6 mm. A similar infarct is present beneath the capsule of the spleen.

Anatomic Diagnosis.—Primary chorio-epithelioma of the fundus of the uterus; metastatic tumor nodules of the lungs; marked anemia; moderate emaciation; low midline superficially infected laparotomy incision; panhysterectomy; generalized fibrino-purulent peritonitis; bilateral serofibrinous pleuritis; infarcts in the kidneys and spleen; sacral decubitus; marked hyperplasia of the spleen; carious and missing teeth.

In microscopic preparations through the primary tumor there are irregularly branching strands of syncytium with small deeply staining nuclei which invade the uterine musculature and blood vessels and line some of the sinuses. Langhans' cells accompany the syncytium as infiltrating masses of large clear cells with vesicular nuclei. The villous arrangement of the syncytium and Langhans' cells is lost. Areas of extensive hemorrhage are present. The musculature is infiltrated with round cells and polymorphonuclear leukocytes. In the metastases the syncytium is found at the periphery of the infarcts, extending in as small isolated clumps. The branching character of the growth as found in the uterus is largely absent in these embolic tumor masses. Langhans' cells are comparatively few.

The question as to the type of this tumor presents itself. Chorio-epitheliomas have been variously classified into the benign and malignant, the typical and atypical and mixed types of Marchand, etc. Ewing presents a classification based on an attempt to group the tumors according to their histologic structure and their degree of malignancy. He subdivides them into four groups.

Group I.—Includes those forms related to and resembling hydatidiform mole. The malignancy is proportionate to the amount of proliferation of the syncytial and Langhans layers. As a rule, this type is relatively benign.

Group II.—Includes the tumors called chorio-adenomas. They correspond to the typical chorio-epitheliomas of Marchand. In this form all the structures of the normal villus are reproduced in an orderly fashion. The Langhans cells are sharply defined and show little tendency to metaplasia. Growth is by extension, rarely by metastases.

Group III.—Termed choriocarcinomas. The tumors of this group correspond to Marchand's malignant chorio-epitheliomas. An extensive proliferation and metaphasia of the Langhans cells and syncytium exists and the orderly arrangement of the tumor constituents is lost. The tumor cells metastasize early and the secondary nodules tend to lose the differential features of the primary growth. Grossly the uterine tumors are small and metastases are numerous in the lungs, brain, spleen and other organs.

Group IV.—Called syncytial endometritis. This group corresponds to Marchand's atypical chorio-epitheliomas. The tumor cells are characterized by an absence of actively proliferating syncytium and Langhans' cells. The uterine musculature and sinuses are infiltrated with numerous large mononuclear cells derived from syncytium and producing a uniformly enlarged and lobulated uterus. Less frequently a large intra-uterine mass is produced. Metastases occur, but less readily than in the tumors of Group III. Transitional forms of these groups may occur.

The tumor in question is malignant, for within six months of the onset of the patient's illness metastases have occurred. The early metastases, the small size of the primary growth and the presence of actively proliferating and metaplastic Langhans cells and syncytium would probably place this tumor among the chorio-carcinomas.

Dec. 10, 1917.

THE EFFECTS OF ALCOHOL ON THE REPRODUCTIVE TISSUES*

ADA HART ARLITT AND H. GIDEON WELLS

Administration of alcohol in the food of male white rats for 2 or more months, in daily quantities of 0.25 to 3 c.c., results almost constantly in the appearance of marked degenerative alterations in the testicles. These changes affect the steps of spermatogenesis in inverse order to their occurrence, so that for some time before sterility and complete aspermia result, the animal is producing spermatozoa with all possible degrees of abnormality and deficiency. The possible relation of this abnormal spermatogenesis to the production of defective offspring is obvious. Individual rats show marked differences in the degree of change produced by equal amounts of alcohol. The fibrous, interstitial and vascular elements of the testicle are not affected, except for intertubular edema compensating for tubular atrophy. These experimental observations harmonize with the necropsy findings in human alcoholics. No other tissue was found to be noticeably affected by the alcohol; especially to be remarked is the absence of cirrhosis or fatty infiltration in the liver.

The changes produced by alcohol seem to take place in quite definite order. At first the spermatocytes seem to be normal in number and appearance, but there is soon noticed an increase in the number of spermatids in the tubules with a decrease in the number of spermatozoa. At the same time, or earlier, there is observed a greater diminution in the number of complete spermatozoa with tails than in the number of sperm heads. Not all tubules in the testicles show the same degree of change, except in the most advanced cases. In the more moderately affected testicles one finds some tubules nearly or quite normal,

* An abstract. The complete article is published in the Journal of Experimental Medicine, 1917, **26**, p. 769.

while others show merely a few active spermatocytes with the lumen packed with spermatids, without spermatozoa or even spermatozoa heads. Apparently the first effect of the alcohol is to render the formation of spermatozoa incomplete, so that the heads are formed without normal tails. In accordance with this, in such a testicle we usually find the number of spermatozoa in the tubules of the epididymis much less in number than normal, and less in proportion than the number of spermatozoa seen in the seminiferous tubules, suggesting that the latter are too imperfect to migrate to the epididymis. The next effect of the alcohol seems to be to prevent the transformation of the spermatids into spermatozoa, whereby the tubules become filled with accumulated spermatids, with but a few spermatozoa or none at all. These spermatids then undergo a process of degeneration, so that they lose their nuclear stain and become granular. In the most advanced stages the tubules contain but the marginal cells, with few or no spermatocytes or spermatids. Occasionally in the lumen of tubules showing advanced degeneration, are found large cells with many nuclei or chromatin masses.

The degree of atrophy does not exactly parallel the decrease in functional activity, but usually the diameter of the tubules corresponds somewhat with the loss of function. When the tubules are atrophied there is commonly some compensatory accumulation of serous fluid in the interlobular spaces—an edema ex vacuo. In no instance have inflammatory changes been seen, and no marked fibrosis, although in some instances there has been an apparent slight increase in the thickness of the basement membrane of the tubules. We have noted no definite multiplication or other changes in the interstitial cells of Leydig, although when the tubules shrink apart these cells become more evident. No arterial changes were observed.

The epididymis generally reflects, in the number of sperma it contains, the degree of functional impairment of the testicle. In two of the rats there was also noteworthy desquamation of the epithelial lining of the ducts. Other changes were not observed in the epididymis.

Although the ovaries of the alcoholized females, and of the offspring of alcoholized parents, were examined in considerable numbers, it is not possible to make any positive statement as to the effect of alcohol on this organ. The changes of ovulation, pregnancy and corpus luteum formation produce such great structural alterations in the ovary that we were unable to determine satisfactorily what changes were caused by the alcohol. There were two distinctly atrophic ovaries found in females that had had alcohol; and in several alcoholic females the ovaries were poor in ova in the sections examined.

Jan. 14, 1918.

CHANGES IN THE BRAIN IN GAS (CARBON MONOXID) POISONING

EMORY HILL AND C. B. SEMERAK

From the Anatomical Laboratory, University of Chicago and the Pathological Laboratory, Rush Medical College, Chicago

Several practical considerations make this a timely subject. Deaths from inhalation of gas, accidental and suicidal, are increasingly frequent; carbon monoxid liberated from bursting shells is a factor in mortality in trench warfare; the possibility of carbon monoxid being a factor in deaths not easily explained is of medicolegal importance, especially if it can be established, as Kolisko maintains, that his gas produces invariably a characteristic lesion in the brain.

Numerous pathologic conditions were found which cannot be attributed to gas poisoning, but certain changes in the 20 brains examined were constant or so frequent that they may be regarded as characteristic of carbon monoxid poisoning.

Carbonylemia.—When death occurs before the carbon monoxid is eliminated from the blood there is a cherry-red color of the leptomeninges and a pink color of the white matter of the brain. These appearances were observed in the majority of our brains. Spectroscopic and chemical tests show that this lighter col-

ored blood contains carbon monoxid. The chemical tests depend on the persistence of a red blood serum or coagulum after carbon monoxid blood has been mixed with various chemicals in contrast to the gray, brown or black color of normal blood treated similarly.

Hyperemia of the Brain and Leptomeninges.—This was observed in every case. No diagnostic importance is attributed to this common appearance in cerebral disease. The upper convexity of the parietal lobes was chiefly involved.

Punctiform Hemorrhages.—These were uniformly observed in leptomeninges and white matter. The corona radiata, centrum semi-ovale, pons and medulla were especially involved. In contrast to the usual predilection for the white matter was the frequent involvement of the dentate nucleus of the cerebellum. The hemorrhages were often so small that only microscopic study could differentiate them from the stippled appearance of hyperemia. We have not found a single instance of hemorrhage in the corpus callosum, which has been described by several writers. Mott considers it characteristic of carbon monoxid poisoning. One must, however, exclude concussion hemorrhage and the influence of other gases than carbon monoxid. Hoover has found hemorrhage in the corpus callosum in trench cases poisoned by phosgene gas, but not in carbon monoxid poisoning.

Edema—This was present in most of the brains which remain soft for a considerable time in contrast to the rapid drying of the moist normal brain. The leptomeninges are cloudy, owing to the precipitate from the edematous fluid. These brains cut with much resistance to the knife.

Bilateral Softening of the Lenticular Nucleus.—This condition was found in every brain. In 12 brains this was evident on gross examination; in 8 more brains it was discovered microscopically. Kolisko has called attention to this localized softening which he considered pathognomonic of carbon monoxid poisoning. We have been able by palpation to select from miscel-

laneous assortments of hardened brains those in which death has resulted from illuminating gas poisoning, with the exception of those in which death had occurred so quickly or the dosage of gas had been so small that only microscopic changes had been produced. The degree of softening varies with age, amount of gas inhaled, duration of life after poisoning, and the previous condition of the blood vessels. In general, younger individuals, more quickly killed, with less preexisting pathology, had slighter changes in the lenticular nucleus. One of these factors may outweigh the others. For example, a man, aged 64, lived 6 weeks and had only microscopic evidence of softening; but he was still conscious when found in a gas-filled room, and therefore could not have had a large percentage of carbon monoxid in his blood. On the other hand, a man, aged 27, who was found unconscious in a gas-filled room and died on the way to the hospital, had gross changes in the lenticular nucleus. He, of course, had received an overwhelming dosage of gas. Comparison of the changes in the brains with the complete necropsy reports shows a considerable correspondence between the damage done by the gas and the amount of disease from other causes. Haldane emphasizes this in his statement that the effects of carbon monoxid are the summation of the preexisting pathologic changes. The necrosis varies from microscopic lesions about the blood vessels to large slushy masses. Three days in formalin is sufficient to bring out the difference between the softened areas and the surrounding hardened tissue. The globus pallidus is always involved. The softening extends to the putamen frequently, and even to the internal capsule, involving the anterior and posterior limbs and knee.

Microscopic examination confirms the gross appearances of hyperemia, edema, capillary hemorrhage and necrosis. The most striking feature of the minute changes is *thrombosis*. Where hemorrhage and perivascular necrosis were seen there were thrombosed veins. Usually the arteries were empty. The capillaries showed damaged or destroyed endothelium,

either lying in fragments in the vessel lumen or absent altogether. Fatty degeneration of the vessel walls has been described by Mott and Poelchen, who consider it the characteristic change produced by carbon monoxid on the blood vessels. We found no evidence of this. The globular masses which they describe are present in our brains, but they do not stain with sudan III. They are 4 to 20 microns in size and occur especially in the granular layer of the cortex just beneath the pia and about the ependymal linings, and around the blood vessels and perivascular lymph spaces in chapletlike groupings. They do not stain with phosphotungstic acid hematoxylin but are a deep purple with hematoxylin and eosin. In places, one makes out all gradations from slightly damaged nerve cells to granular fragments of these cells with a faint nucleus seen only with the high power, and the homogeneous spherical bodies described. The oil immersion shows in some of these a lamellation which suggests the corpora amylacea of the prostate. Whether these are postmortem changes or degeneration products of a hyaline or amyloid nature we cannot say; but we do not believe that they represent fatty degeneration.

Nerve Cells.—These seem to have a high degree of resistance to the gas. In places they are severely damaged or destroyed, but more often the comparatively normal nerve cells in and about an area of hemorrhage or necrosis present a striking picture. The most frequent change observed was chromatolysis of the Nissl bodies and excentric position of the nucleus.

Several questions arising in this study require further investigation. The conclusions reached so far are that carbon monoxid produces pathologic changes depending largely on preexisting conditions of the blood vessels. The constant minimum change is thrombosis of the veins in the globus pallidus with consequent ischemic necrosis. Usually the necrosis is sufficient to produce a softening evident to the palpating finger. Frequently the softening extends to the putamen and internal capsule as well. Thus, bilateral softening of the lenticular nucleus may be considered the characteristic sign of carbon monoxid poisoning.

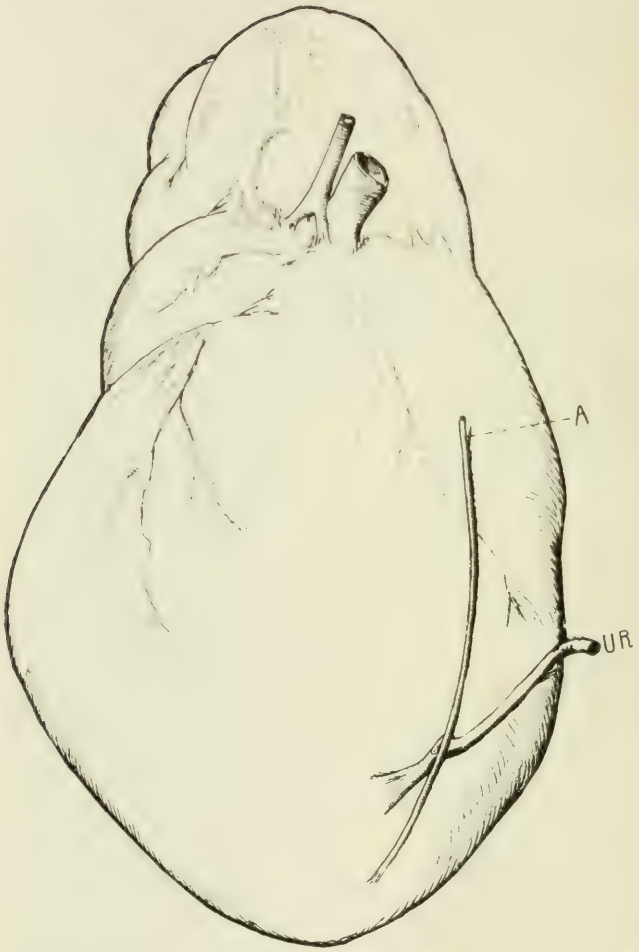
Jan. 14, 1918.

AN UNUSUAL HYDRONEPHROSIS WITH UREMIA, DUE TO AN ANOMALOUS RENAL ARTERY

JOHN D. ELLIS

From the Pathological Laboratory, Rush Medical College, Chicago

A German, aged 74, was admitted to the service of Dr. Hall at the Cook County Hospital with an examining room diagnosis of epilepsy. He was brought by the police ambulance from a station where he had been found semiconscious several hours before. A history was obtained from his daughter, that for the past six years he had had epileptiform convulsions, also mental disturbances including delusions of grandeur and loss of memory. A diagnosis of "softening of the brain" had been made by a physician. Examination was difficult because of the excitability of the patient. He was unable to talk and seemed violently insane. When approached, he screamed and attempted to kick and strike. He appeared to be about 65 years old. Respiration was 26; pulse slow and of high tension; systolic blood pressure 180 mm. Hg. There was no sign of injury of any part of the body. The pupils were unequal, contracted, with irregular margins, and did not react to light. There was venous engorgement of the neck. The lungs were resonant with normal boundaries. Moist râles were heard everywhere over the lungs except in the apices, which were clear. The transverse dulness of the heart was increased; the apex beat in the 6th interspace 11 cm. from the midsternal line. There was a systolic apical murmur with the second sound accentuated. The abdomen was rigid. There were varicose veins of the legs but no edema. The reflexes except those of the eyes were normal. The blood Wassermann was negative. Attempt at lumbar puncture gave a dry tap. While in the hospital, the pulse varied from 80-98, the temperature from 98-100.4 F. On the day after entrance he was still maniacal, weaker and he had two clonic convulsions, the longer lasting 10 minutes. The next day not having micturated for 36 hours he was catheterized and 500 c.c. of clear amber-colored urine of a specific gravity of 1.020, containing a trace of albumin, and free from sugar, was obtained. The mucus râles in the lungs increased; the systolic pressure fell to 80 mm. Hg; the heart dilated. He died 49 hours after admission.



View of kidney from the lower inner aspect. *U R*, ureter; *A*, anomalous renal artery supplying lower pole.

Anatomic Diagnosis.—Unilateral huge hydronephrosis with atrophy of the right kidney (uremia); senile sclerosis of the aorta, coronary and cerebral arteries; atheromatous ulcers of the aorta; marked sclerosis of the aortic valves; marked hypertrophy of the heart; marked edema and hyperemia of the lungs; passive hyperemia of the liver, spleen, pancreas and small bowel; slight anasarca; edema of tracheobronchial lymph glands; small superficial varicose veins of the legs and back of the tongue; disseminated focal atrophy (arteriosclerotic) of the cerebral cortex; anemia and emaciation; healing superficial abrasions; old healed calcified empyema of the right lung; fibrous pleuritis; fibrous pericarditis; marked external fibrous mediastinopericarditis; hypostatic hyperemia of the rectum and urinary bladder; lessened yellow material of the adrenal cortices; hyperplasia of the thyroid gland (colloid goiter); external fibrous leptomeningitis; fibrous atrophy of the tonsils; fibrous capsular perisplenitis; calcified nodules in the liver and spleen; coal-dust pigmentation of the biliary and tracheobronchial lymph glands; calcified tracheobronchial lymph glands; ossified costal cartilages; slight external fibrous pachymeningitis; canites; exostosis of the lumbar vertebrae; adventitious (developmental) fibrous adhesions between the mesosigmoid and abdominal wall; multiple subcutaneous lipomas; long since absent teeth; scars of the chest.

"On the right side of the abdomen there is a cyst projecting below the margin of the liver 10 cm. From its lower surface the ureter apparently descends. The cyst is adherent to the lower surface of the liver. The colon has to be dissected away from it. It is 9 cm. wide. The inferior cava is also a little adherent to the inner margin. After the removal of the bowel the cyst is found to be much larger than examination from the front indicated. Lying on a flat surface it is 19 by 16 cm. and it consists of two portions, an elongated pear-shaped mass on the outside, and the cyst already described on the inside."

The cyst after fixing in formalin weighs 1,075 gm. and is irregularly divided into fluctuant cavities, the largest 14 by 11.5 cm., in the lower pole representing the dilated pelvis. The remainder of the kidney consists of 18 or 20 similar fluctuant masses. On the rough, white, fibrous surface are many tags of broken adhesions. The thickened, fibrous capsule cannot be detached. The vessels of the capsule have enlarged. On cutting, the entire fluid content, 925 c.c., colorless and with a specific gravity of 1.020, escapes from the thin walled cavities of which the kidney is composed. These communicate with each other and have a smooth glistening

white lining, and walls 1-2 mm. thick, in some places almost transparent. The ureter opens from the lowest part of the dilated pelvis by a transverse slit 2 cm. long, from which it runs as a flattened cone inward along the surface of, and closely adherent to, the dilated pelvis for 1 cm. and at the distal end of this 1 cm., the diameter of the ureter is 1.8 mm. Here it is crossed by an anomalous renal artery which comes down in front of the ureter, unaccompanied by a vein, crosses the ureter at an angle of about 5 degrees and passes into the fibrous covering of the renal pelvis behind the origin of the ureter. It is closely adherent to the ureter where the two cross. The ureter passes over the artery with an angulation so that the lining of the ureter is bent up in a typical valvelike spur. When the ureter is split open no narrowing of the lumen is found here.

"The left kidney has a cortex lessened by one-third, its average width being 3-5 mm. The capsule strips easily, leaving a finely granular surface. The ureter is unaltered. The renal artery is uniformly thick walled but otherwise unchanged. This kidney weighs 180 gm."

In microscopic preparations from the cortex of the right kidney the changes characteristic of pressure are present.

A valvelike fold or spur such as that in this ureter is present in a large percentage of the cases of acquired hydronephrosis and before the work of Fenger[1] was generally regarded as the direct cause of the retention of urine in the pelvis and subsequent development of hydronephrosis.

In 1900, however, Fenger pointed out that this fold at the ureteropelvic junction suggestive of valve formation might well be a result of hydronephrosis and not the cause of it. He illustrated this explanation by a diagram showing how dilatation of the end of a closed tube, unless this process was entirely symmetrical, would result in the formation of a valvelike spur at the junction of the unchanged tube with the dilated part.

In the decade following Fenger the current of opinion as to the relative frequency of valve formation and of anomalous vessels as causes of the development of hydronephrosis changed. Writers began with increasing frequency to report cases of hydronephrosis

1. Arch. f. klin. Chir., 1900, **62**, p. 528.

caused by anomalous renal vessels passing across the ureter close to its junction with the pelvis. In the same year that Fenger's work appeared Israel (cited by Fenger) described compression of the ureter by a posterior branch of the renal artery as well as its operative remedy. In 1907, Ekehorn[2] in a study of 25 cases of hydronephrosis found accessory vessels anterior to the ureter in 64% and posterior in 28%. Mayo[3] in 20 out of 27 consecutive cases operated on for hydronephrosis found anomalous blood vessels obstructing the ureter by crossing it at the junction with the pelvis. "These vessels pass to the lower pole of the kidney and vary in size from that of a knitting needle to a radial artery." Seventy-five per cent. of these vessels passed in front of the ureter. To prove that these blood vessels were the cause of the hydronephrosis, it was shown that in 13 of these cases, severing of the anomalous vessels sufficed to remedy the condition. Levings[4] reported 4 cases operated on in which arteries were divided with improvement of the clinical symptoms. Rupert[5] and McDonald[6] have studied the occurrence of anomalous renal vessels in the dissecting room and the former found them in 35 out of 50 cadavers, not all, however, at the lower pole of the kidney, the position where they are most likely to be a factor in the angulation and constriction of the ureter. McDonald is of the opinion that at least three factors may be associated with an anomalous vessel in the causation of hydronephrosis.

"1. If there is a dilatation for any cause such a vessel coming in relation to the dilated ureter might cause an angulation or stricture and represent the beginning of a hydronephrosis.

"2. Inflammatory adhesions about the pelvis or ureter might be a factor, with an aberrant vessel, in causing dilatation of the ureter above a stricture.

2. Arch. f. klin. Chir. (Langenbeck's), 1907, **82**, p. 955.
3. Jour. Am. Med. Assn., 1909, **52**, p. 1383.
4. Wisconsin Med. Jour., 1914, **10**, p. 555.
5. Surg., Gynec. and Obst., 1913, **17**, p. 580.
6. Ann. Surg., 1910, **52**, p. 814.

"3. Mobility of the kidney may become an important factor. In a simple nephroptosis, the ureter might form a kink over an aberrant vessel."

He believes, however, that if the vessel is in front of the ureter, such a kinking cannot occur unless the kidney should fall forward. This reasoning is in line with that of MacCarty,[7] who thinks that the development of hydronephrosis in association with anomalous vessels is primarily determined by some such factor as diminution of the perirenal fat, or general laxity of abdominal organs as may occur after pregnancy or illness, allowing the kidney to move down so that these vessels form a suspension bridge over which the ureter hangs. "At the point of suspension the ureter is bent on itself forming a kink. As the angulation becomes more acute, the approximating sides of the ureter form a valve."

In this instance I have studied, while there is no conspicuous ptosis of the kidney, there are, about the intersection of the ureter and artery, well marked adhesions.

A more important contribution than such speculation is the experimental production by Scott,[8] Snowden,[9] Keith and Pulford,[10] of hydronephrosis in dogs by partial constriction of the ureter with rubber bands which may be considered to compare closely to the compression of the ureter by the elastic blood vessels. There is a significant similarity between the clinical history of our case and that of several of the dogs used by Keith and Pulford in which renal insufficiency developed suddenly many months after the partial obstruction of the ureter had been pronounced.

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7. Jour. Am. Med. Assn., 1909, **52**, p. 1386.
8. Surg., Gynec. and Obst., 1912, **15**, p. 296.
9. Arch. Int. Med., 1915, **15**, p. 239.
10. Arch. Int. Med., 1917, **20**, p. 1886.

SUDDEN DEATH FROM (1) MINUTE SPONTANEOUS HEMORRHAGES IN THE PONS AND MEDULLA; AND (2) SYPHILITIC MENINGOMYELITIS

C. B. SEMERAK

From the Pathological Laboratory of Rush Medical College, Chicago

Case 1.—A man, aged 30, was brought to the Cook County Hospital with the history of having fallen in a fit while working. On admittance to the hospital the patient was in deep coma; the right side of his body was paralyzed, the respiration slow, pulse irregular and weak; the region of the heart dulness was enlarged and murmurs could be heard at the apex. He gradually weakened and died without regaining consciousness two days after his admission to the hospital.

The clinical diagnosis was mitral stenosis and cerebral embolism which the postmortem examination by Dr. E. R. LeCount confirmed.

The brain was removed and put in a solution of formaldehyd to harden, and on examination about a month later, the following changes were noted:

The vessels of the leptomeninges are greatly engorged with their finer radicles standing out sharply.

The brain is more resistant on cutting than the average normal brain and the cut surfaces are pale.

The lateral ventricles are dilated and measure 9 mm., transversely in their largest dimension, at the anterior commissure.

The septum pellucidum is split throughout its whole length.

In the central portion of the pons, a few mm. to the left of the midline there is a hemorrhage, 2 mm. long, 3 mm. wide and extending 6 mm. anteroposteriorly. A few minute punctiform hemorrhages are also seen at the floor of the fourth ventricle.

Anatomic Diagnosis: Spontaneous miliary hemorrhages in the pons and medulla; edema and anemia of the brain; internal hydrocephalus; hyperemia of the leptomeninges.

Outside of those minute hemorrhages, which are so small as almost to escape attention, nothing could be detected to which sudden death might be attributed.

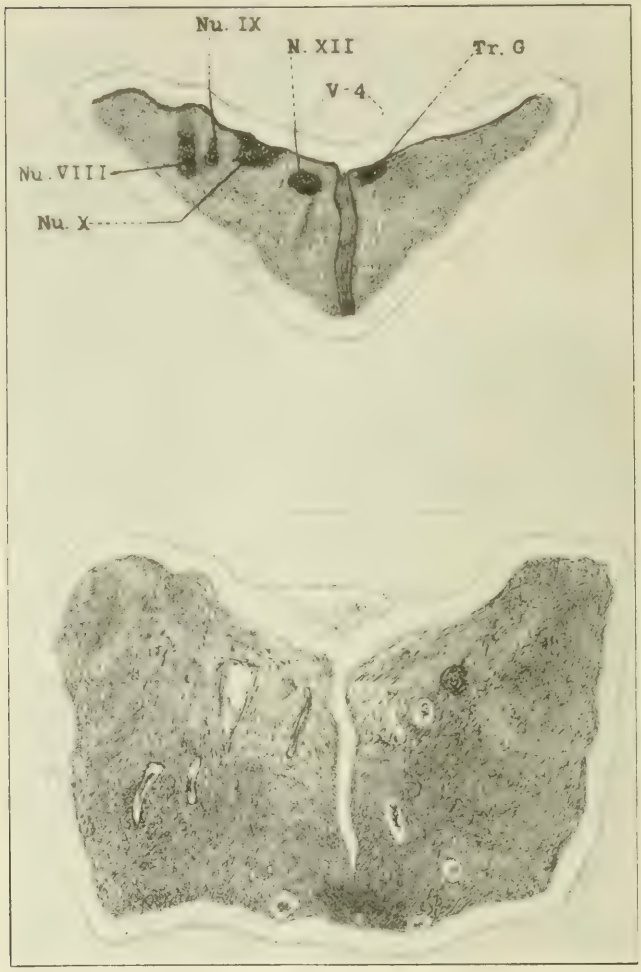

Fig. 1.—Cross-section of normal medulla.

Nu VIII. Nucl. N. Acustici.
Nu X. Nucl. Dorsalis Vagi.
Nu IX. Nucl. N. Glossopharyngei.
Nu XII. Nucl. N. Hypoglossi.
Tr. G. Tractus gracilis.

In order to determine the extent and degree of the lesion, microscopic examinations were made from various regions of the pons and medulla.

The whole brain stem is found to be peppered with capillary hemorrhages which could not be detected with the naked eye. Erythrocytes are seen to infiltrate the tissue throughout. The walls of many vessels are broken and segmented and perfused with blood elements. Some larger vessels are extremely distended and hyperemic, while others are empty and collapsed.

There are large regions of necrosis in the hemorrhagic area; the large nerve cells are diffuse in contour, some have undergone hyaline degeneration, some others are completely covered with dark yellow pigment.

The ependyma of the fourth ventricle and of the aqueduct of Sylvius is torn and the endothelial cells are scattered.

The fasciculus longitudinalis posterior, the corpus restiforme and the region of the oculomotor, trochlear and trigeminus nuclei with the lateral and medial lemnisci and part of the pontical fibers are involved in the necrosis and the hemorrhage.

In all the degenerated regions, in the subpial layer and in the immediate vicinity of the fourth ventricle and aqueduct of Sylvius there are numerous amyloid (?) bodies varying in size from 10 to 20 microns and staining a deeper blue with alum hematoxylin than the nuclei.

Spontaneous hemorrhages in the brain are of quite frequent occurrence and sudden death results in many cases when vital centers are involved or when the hemorrhage has been very extensive. As a rule the corpus striatum and the thalamus are the seat of predilection, less frequently the occipital lobes, the corpus callosum, the pons, and the cerebellum. Pontine hemorrhages are often found secondary to hemorrhages elsewhere in the brain (Greenacre[1]), but primary spontaneous hemorrhage in the pons and medulla are said to be rare; from necropsies made at the Bohemian Medicolegal Institute in Prag where out of 1,242 cases of sudden death, 73 were due to hemorrhage in the brain, of which only two were spontaneous hemorrhages in the medulla and pons (Slavik[2]).

1. Bull. Johns Hopkins Hosp., February, 1917.
2. Ætiologie Nahleho Umrti, Prag, 1902.

However, this has not been the case in the experience of Dr. E. R. LeCount, who has met with several hundred pontine hemorrhages.

Spontaneous hemorrhages in the brain are as a rule extensive and are caused by pathologic changes in the vessel walls, atheromatous or others, or pathologic changes in the brain tissue, glioma, encephalomalacia, tuberculosis, etc.

The so-called miliary hemorrhages are not as a rule the cause of sudden death, unless very numerous. They are said to occur when there is sudden stoppage in the circulation, or are due to alcoholism, miliary tuberculosis, hemorrhagic diathesis and various infections and poisons.

Case 2.—A Greek laborer, aged 43, was taken to the Cook County Hospital from his home; his friends said he had become nervous and weak during the morning. One friend told the deputy coroner that the patient had been sick for a long time, troubled mostly with headaches. No other history was available because of lack of an interpreter.

Physical examination showed a restless, icterus colored, apathetic looking patient who complained of not being able to keep his eyelids open. The protruding tongue deviated to the right. There was a paresis of the right leg muscles and the triceps and biceps of the arm and flexors of the fingers. The right upper quadrant of the abdomen was tender.

The right-sided paralysis became more marked and spastic in character and two days later the patient died.

The postmortem examination was made by Dr. E. R. LeCount. It revealed: Anemia of the brain; syphilitic scars of the leptomeninges; fibrous perivascular leptomeningitis; marked sclerosis of the coronary arteries; sclerosis of the cerebral arteries; minute petechial hemorrhages of the lining of the left ventricle of the heart; petechial hemorrhages of the lungs; the stomach, the duodenum, and visceral pleura; calcified and caseous tuberculosis of the lungs, bronchopneumonia.

The brain was removed and preserved in formaldehyd and after one month a thorough examination was made.

There are pits in the cerebral cortex, over both the frontal lobes, measuring 6 to 10 mm. in diameter. The arterioles of the leptomeninges are greatly engorged and their radicles stand out sharply. The leptomeninges of the cephalic portion of the frontal lobes are stained diffusely reddish brown, and studded with multiple, white fibrous thickenings, forming

either rows or large patches in the sulci, especially in the left superior frontal sulcus.

At the base of the right superior frontal gyrus there is an old yellow bruise about 1.5 cm. long and 1 cm. wide, where the leptomeninges are missing.

The arteries of the base of the brain are thickened and glistening and gaping. The surfaces made by sectioning the brain have a markedly stippled appearance in the gray and white matter.

The ependyma is thickened and granular. The lateral ventricles were distended and measure 12 mm. transversely in their largest dimension at the anterior commissure. There are no other gross changes.

Anatomic Diagnosis: Disseminated atrophy of the cerebral cortex; hyperemia of the brain and leptomeninges; circumscribed intrameningeal hemorrhage; disseminated syphilitic leptomeningitis; internal hydrocephalus; plaques jaunes; granular ependymitis.

Sections were made from various parts of the brain for microscopic examination as follows:

Cortex: There was a rarification of the cellular elements in the granular layer; a great number of the nerve cells are ill-defined in outline with a markedly swollen nucleus and little protoplasm. In many cells the nucleus cannot be made out, the whole cell being filled with a mass of granules. In the layer of large pyramidal cells there are several regions where all nervous elements have disappeared and been replaced by a dense layer of round cells and vacuoles. The endothelium of most of the capillaries is in an active stage of proliferation.

Floor of the Fourth Ventricle. The tissue is markedly fenestrated and necrosed; there are wide-meshed fibers containing numerous blood vessels, some minute capillary hemorrhages and degenerated cells. Other small hemorrhages are seen also more ventrally in the less degenerated part. Most of the larger neurons have undergone retrogressive changes; some are filled with fine pigment granules; some stain homogeneously with no trace of nucleus left.

Throughout the degenerated tissue are scattered multiple amyloid bodies of various sizes (8 to 25 microns).

The degeneration involves the nucleus dorsalis vagi, nucleus vestibularis, nucleus nervi hypoglossi, nucleus and tractus solitarius, fasciculus longitudinalis medialis and structures of less vital importance (see Plate 1). It extends down the spinal cord into the fasciculi gracilis and cuneatus but is less marked and more diffuse, involving also the lateral and ventral portions of the spinal cord.

There is a dense infiltration of lymphocytes throughout the pia-arachnoid over the cerebrum, the medulla and the spinal cord. The vessels of the cortex and the leptomeninges are about twice as thick as normal and are sclerosed and surrounded by several layers of lymphocytes, which in various regions form large clusters of 10 rows or more.

In the anterolateral medullary region there is a large sclerotic meningeal vessel, the intima of which is about five times thicker at one side, the thickening protruding into the lumen and consisting of fibrous tissue, endothelial leukocytes and plasma cells in between the meshes. The adventia is also thickened and presents active inflammatory and productive changes. The lumen of some vessels of the spinal membrane is completely obliterated by concentric layers of connective tissue. Other vessels are partly filled with endothelial leukocytes and lymphocytes. Most of the finer arterioles and capillaries have lost partly or completely their endothelium. The pia adheres closely to the arachnoid which latter is enormously thickened in places, and to the cortex. Its meshes are closely packed with lymphocytes, granular precipitate and broken endothelial cells.

The tissue in the cervical region of the spinal cord immediately adjoining the medulla is necrosed, greatly vacuolated, and the cellular elements are rare.

Diagnosis: Marked degenerative changes in the medulla and spinal cord; minute hemorrhages in the medulla; marked sclerogummatous cerebrospinal leptomeningitis; obliterating syphilitic endarteritis; marked proliferating syphilitic periarteritis.

Sudden death due to syphilitic changes in the spinal cord is rare. Generally it is caused by inflammatory changes in the vertebrae which compress and traumatize it; sometimes rupture of an abscess (Pott's disease) is the cause of sudden death (Herteaux) and sometimes multiple and sudden hemorrhages in the leptomeninges, most frequently due to trauma.

Myelomeningitis syphilitica is in itself a rather rare condition which may manifest itself either by circumscribed plaques or scars or by diffuse infiltration of the meninges, and which may involve to a greater or less extent the tissue of the medulla and spinal cord. Partial or complete necrosis of the surrounding tracts or cells follows, produced either from the pressure of the exudate or scar tissue or from insufficiency of the blood supply due to the obliterated vessels.

Jan. 14, 1918.

BALANTIDIAL COLITIS *

C. H. MANLOVE

CHICAGO

(From the Department of Pathology and Bacteriology, University of Illinois.)

Balantidial colitis with fatal termination can scarcely be called common in the Philippines although the presence of Balantidium coli in man in the Philippines is rather common. Reference was made to experimental balantidiasia in which Balantidium coli suis and Balantidium coli hominis were proven identical and that infection took place through a normal mucosa in monkeys fed with balantidia.

At necropsy the walls of the colon are somewhat thickened and the mucosa is more or less ulcerated throughout its entire length. The ulcers may be divided into three stages according to the degree of involvement of the colon wall: an early, medium, and late. All three stages are found throughout the entire colon, but predominate as follows: Those in the cecum are mostly in a late stage with some early and medium found here and there; those of the rectum are mostly of the medium stage with the late stage next in frequency; those of the transverse colon are of all three stages, of which the medium predominates.

The balantidia in relation to the mucosa are found on the surface, in the tubules of the glands, within the glandular walls, in apposition to the muscularis mucosa, just penetrating the glandular basement membrane, in the superficial ulcers, and in the solitary lymphoid follicles. They are found both in direct relation to ulcers and in mucosa which is not in close contact with ulcers. In no instance is there any definite cellular reaction surrounding a singly located organism.

Two clinical histories were given of the two cases reported.

* The complete report is found in The Philippine Journal of Science, Vol. 12, No. 3, Sec. B, Tropical Medicine, May, 1917.

DISCUSSION

In one of the reported cases there was broncopheumonia and a pleuritis with flocculent fluid material in the pleural sac. Care was taken to exclude the possibility of balantidial involvement of the lung and pleura. In view of the fact that the sections of the colon show balantidia in blood vessels there must be a continual entrance of balantidia into the general circulation. However, it is rare to find them producing lesions outside of the intestines, although they have been reported in sputum from a case of supposed lung involvement.

Since the balantidia are found penetrating both the mucosa and submucosa without any surrounding cellular infiltration, it may be safely concluded that they are capable of penetrating apparently healthy mucosa. Here they may produce sterile abscesses which may in time become secondarily infected by the rupture of the mucosa covering them and thus form ulcers. Macroscopically, the lesions produced by Balantidium coli cannot be differentiated from those of Entameba histolytica. Microscopically, the lesions show a similar reaction, but are easily differentiated by finding the organisms.

The question of the essential pathogenicity of balantidia is an important one, and one which cannot yet be considered to be absolutely settled. Reasoning from analogy with known facts concerning the action of entamebae, and from the known tissue changes described in balantidiasis it seems necessary to believe that their action is in all ways similar to the action of the entamebae.

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OBSERVATIONS ON BACTERIOLOGY OF RUBEOLA (MEASLES) AND RUBELLA (GERMAN MEASLES)

RUTH TUNNICLIFF

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I[1] have previously described a small, round, gram-positive, diplococcus, which was isolated from the blood of measles patients during the pre-eruptive and early eruptive stages of the disease, at which time the virus of measles is present in the blood (Hektoen, Anderson and Goldberger). These diplococci were found in largest numbers a few hours before the appearance of the eruption and disappeared when the rash began to fade. They were isolated in anaerobic cultures in 42 of the 50 patients studied, generally in semicoagulated horse serum and ascitic dextrose-agar shake cultures. The cocci grew aerobically in sub-cultures and produced small, green colonies on blood-agar plates. Similar diplococci were isolated from the throat, nose, eye and ear. Cultures of this organism passed through a Berkefeld "N" filter, resisted drying 24 hours, and were killed by heating at 56 C. for 45 minutes. The diplococcus was virulent for laboratory animals, but did not produce the symptoms of measles.

Similar blood cultures have been made from 11 German measles patients, before the eruption began to fade. Anaerobic plates, as used by Dick and

1. Jour. Am. Med. Assn., 1917, 68, p. 1028.

Henry[2] have given the most satisfactory results. Cultures were made in plain or dextrose agar without ascitic fluid. A fairly large, elongated, gram-positive diplococus with pointed ends and a capsule has been grown in cultures from 9 of the 11 patients. They were not present in the blood of 4 patients who had fading eruptions. Only one or two colonies grew on each plate. Throat smears and cultures showed diplococci similar to those isolated from the blood.

The colonies appear on the anaerobic plates after from 1-5 days' incubation, as indistinct, greenish-brown colonies. The cocci become aerobic in the second generation and grow in 24 hours. The colonies are generally small and green on blood agar. Cultures of this diplococcus do not pass through a Berkefeld "N" filter, resist drying 5 days and are killed by heating at 65 C. for one-half hour. These diplococci are not pathogenic for rabbits.

Various immunity tests have been made with the cocci isolated from measles and German measles to determine if any antibody reaction could be demonstrated. So far opsonins have been the only antibodies found in any appreciable amount. The serum of measles patients shows a negative phase followed by a distinct rise in opsonins for the measles diplococcus as the symptoms subside and the eruption disappears, but shows no change for the German measles organism. The German measles patients show just the reverse opsonic content in the blood, showing typical opsonic changes for the German measles coccus but none for the measles organism. There were no changes in the opsonic content of the blood of either measles or German measles patients for Streptococcus viridans, pneumococci or the poliomyelitis coccus, in any of the serums examined. The results indicate that specific opsonins for the measles and German measles diplococci develop during the course of these diseases, disappearing with the recovery of the patient.

The special points of interest in this work are:

2. Jour. Infect. Dis., 1913, 12, p. 199.

The almost constant presence of diplococci in the blood of measles and German measles patients and their presence at the same time in the throat. While the two organisms are similar in their cultural characteristics, they differ in size, shape, capsule formation, filtrability, virulency, viability and immunity reactions.

March 11, 1918.

A STUDY OF PRECIPITIN REACTION IN THE URINE IN PNEUMONIA

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From the John McCormick Institute for Infectious Diseases, Chicago

The author has made a study of the sputum for the type of infection and of the urine for precipitin reactions in 100 cases of lobar pneumonia due to the pneumococcus which occurred in Chicago during the past winter. His results are briefly as follows:

It appears that a large percentage of fatal cases of pneumonia have a substance in the urine capable of giving a specific precipitin reaction with antipneumococcus serum, but that the presence of this substance in the urine is not of great unfavorable prognostic value, as the mortality in those patients in whom it could not be demonstrated was only slightly lower than in those in whom it was present. In every instance in which a precipitin reaction occurred it was specific for the serum corresponding to the type of organism present as determined by agglutination of the pneumococcus isolated from the sputum. When this reaction is present in the urine it is an accurate means, and, at present, the most simple and rapid means of type determination, and is, according to these results, present in 81 per cent. of cases due to Type I, II and III infections, although not always sufficiently early to warrant neglect of the sputum examination for the type of infection.

March 11, 1918.

SPOROTRICHOSIS FOLLOWING MOUSE BITE, WITH CERTAIN IMMUNOLOGIC DATA

JOSIAH J. MOORE AND DAVID JOHN DAVIS

From the Department of Pathology and Bacteriology, University of Illinois College of Medicine, Chicago

Sporotrichosis occurs spontaneously in the horse, mule, dog, rat and man. The disease nearly always follows an injury to the skin, usually a puncture, wound or an abrasion. Lutz and Splendore in Brazil noted that the disease in rats was transmitted from animal to animal by bites or scratches. In the human the diesase has been observed following the bites of the horse, hen, rat, dog and parrot. Whether the organism in these instances or in our own case came from the animals or from some other source cannot be determined with certainty. Sporotricha have been found in the mouths of animals.

A boy, aged 13 years, was bitten on the index finger of his left hand by a field mouse about Sept. 10, 1916, while spending his vacation on a farm near Belfield, N. D., on the Little Missouri River. The wound bled at the time but was apparently healed in a few days. About two weeks later he noticed a swelling of the finger at approximately the point of the old bite wound. This increased until the entire terminal phalanx was swollen, reddened, and firm, but not very painful. A few days later the lesion opened and a purulent discharge appeared. Later nodules appeared along the arm and also one on the opposite arm and on the opposite leg near the knee.

Potassium iodid, 30 grains per day, was given and was followed by marked improvement, but the patient refused to take it until complete cure was established. At the present time the original lesion has healed completely but a sporotrichotic sinus still exists near the base of the finger (1½ years after the initial

infection). Cultures made repeatedly from the ulcer, from the nodules, and from the sinus have yielded Sporotrichium schenckii. The organism is pathogenic for rats and mice.

Tests of sporo-agglutination of the patient's serum have been made from time to time. At first the agglutinins were found at dilutions of 1 : 320. As the patient improved, they became less ; then, with exacerbation of the infection, they increased. At present, specific agglutination occurs at a dilution of 1 : 60.

Several strains of sporotricha including the original Schenckii-Hektoen strain, a strain from Gougerot of Paris, and one from K. F. Meyer isolated from a horse, as well as several American human strains, were tested and all agglutinated at approximately the same dilutions. Two strains of blastomycetes were not agglutinated at 1 : 10.

Complement fixation tests were made using antigens made from the strains mentioned in the foregoing. Positive results were obtained early. As the patient improved, fixation became less and later practically disappeared. This test is apparently not as delicate as the agglutination test. All the antigens served equally well for fixation.

Intracutaneous tests were applied with sporotrichins made by suspending 4 weeks' old cultures in salt solution and killing them by heating at 100 C. for 10 minutes. About 2 drops of a faintly milky suspension were injected. A very marked local specific reaction appeared in 24-48 hours, the diameter of the area being from 5-7 cm. Controls on normal individuals measured about 0.5 to 0.8 cm. A blastomycin made in the same way gave reactions little more than salt solution (0.6-0.8 cm.). Sporotrichins made with American and French strains behaved quite alike. The administration of potassium iodid to the patient and to 4 normal persons caused little difference in the intensity of the intracutaneous reactions.

March 11, 1918.

TRAUMATIC EVULSION OF THE GALLBLADDER

C. J. PEARSALL

O. B., man, aged 58, and a railroad employe, was admitted to the Cook County Hospital, to the service of Dr. Thompson, because of injuries received when struck by a street car. No history was obtained, as the patient was in coma on entrance and did not regain consciousness before death, twenty-four hours later. There were many external bruises and abrasions, especially about the head and shoulders; two lacerations of the scalp; and profuse bleeding from the nose and mouth.

The alterations found at postmortem (Dr. E. R. LeCount) which pertain to this report are as follows: "Traumatic comminuted fracture of the skull, and the first two right ribs, traumatic rupture of the liver, right adrenal and kidney; traumatic evulsion of the gallbladder; huge hemoperitoneum; contused brain; traumatic hemorrhage of the leptomeninges; traumatic extradural hemorrhage; moderate secondary anemia; traumatic hemorrhage of the deep scalp tissues; external bruises, abrasions, and lacerations of the body."

When the abdomen was opened by the usual midline incision, 960 gm. of fluid blood filled the peritoneal cavity. The gallbladder was found floating in the blood in the upper right quadrant of the abdominal cavity, attached only by its pedicle of ducts and blood vessels. It was markedly distended, containing 65 c.c. of bile. There was considerable hemorrhage in the tissues about the right kidney and adrenal, also about the pancreas, duodenum and stomach.

In the center of the groove of the gallbladder on the under surface of the right lobe of the liver there was a tear, 7.5 cm. long, extending from the front margin of the liver to the neck of the gallbladder. It also extended up on the front surface of the liver 3 cm. The tear was irregular, gaping 1 to 3 mm. and the edges were agglutinated with clotted blood (Fig. 1). By cutting the liver into sagittal sections, 2 cm. thick, the rupture was found to extend into the liver substance 2-6 cm., the greatest depth being at the neck of the gallbladder. Here as the tear entered the liver substance it broke up into fine radiating lines, surrounded and running along the course of the larger portal vessels. The periportal liver tissues for 1-3 mm. about these tears was infiltrated with

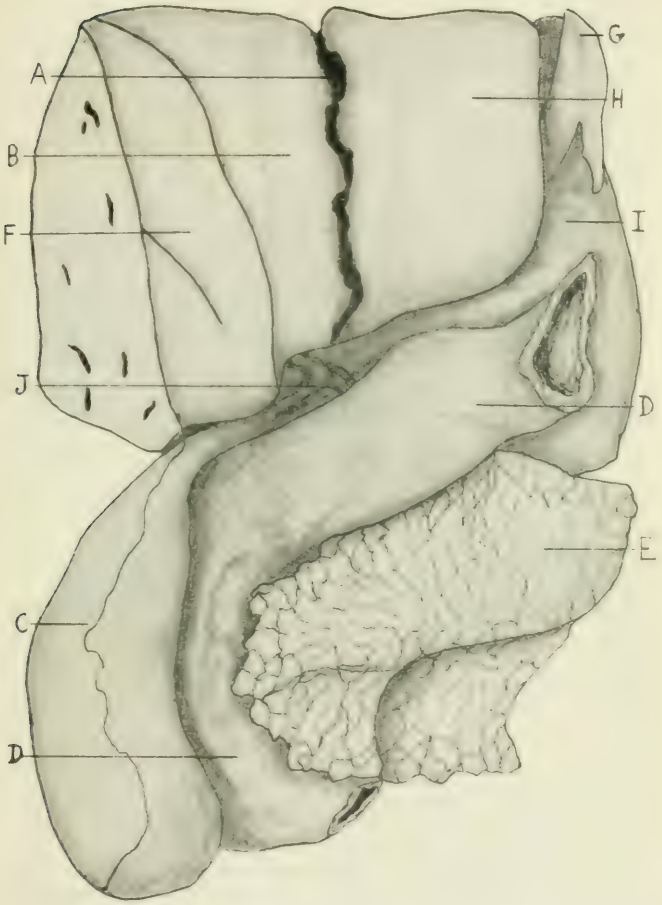

Fig. 1.—The liver is turned up, allowing the gallbladder to hang by its pedicle. (*A*) rupture of the liver; (*B*) groove for gallbladder; (*C*) gallbladder; (*D*) duodenum; (*E*) pancreas; (*F*) right lobe of the liver; (*G*) ligamentum teres; (*H*) quadrate lobe of the liver; (*I*) left lobe of the liver; (*J*) portal vein, hepatic artery, bile ducts, etc.

blood, dark red and a little softer than the uninjured tissue (Fig. 2). At one point a small clot of blood in the periportal tissue partially occluded the lumen of the vein, but in no place were any of the large vessels torn.

The gallbladder was intact and uninjured in any way, as were also the blood vessels and bileducts. There were no antemortem thrombi in any of the vessels about the hilus of the liver.

In direct line with this rupture of the liver there was a tear completely across the middle of the right adrenal. The cortex of the adrenal was infiltrated with blood, the medulla filled with a blood clot.

Just beneath this tear of the adrenal, there was a tear in the upper pole of the right kidney, extending 1.2 cm. down on the front surface, but only through the capsule of the kidney.

Traumatic rupture of the liver from nonpenetrating wounds is not uncommon. Associated with simultaneous rupture of other abdominal viscera, Thöle[1] states that the right kidney and spleen are most frequently injured. He makes no mention of the accompanying injury of the adrenal or gallbladder. Sherk,[2] in 293 subcutaneous injuries of abdominal viscera, found the liver involved in 22 cases, none with accompanying injury of the adrenal. Amante[3] places the incidence of simultaneous subcutaneous rupture of the liver and adrenal as very rare, and also makes no mention of any gallbladder complications in the cases he reported. Geill, cited by Amante, reports 79 cases of partial or complete detachment of the gallbladder in 296 cases of subcutaneous ruptures of the liver; 45 with rupture of the right and left lobes of the liver, 20 in the corresponding fossa of the gallbladder, and 14 in the median line. Amante, in commenting on traumatic evulsion of the gallbladder, states that although it is rare, it is occasionally seen accompanying rupture of the liver; and mentions cases cited by Rastoul, Welms, Francis, Durante and others. The detachment may be partial or complete, as was the case in this instance, the gallbladder remaining attached to the liver by the cystic duct. Amante further states that in order to get complete detach-

1. Die verletzungen der Lebar und der Gallenwege, 1912.
2. Jour. Am. Med. Assn., 1911, 56, p. 718.
3. Le Lesioni Traumatische del Fegato e delle Vie Biliari, Rome, 1912.

ment of the gallbladder from the liver, it must be moderately distended with fluid; then when great force is applied to the surface of the gallbladder it is torn from its normal attachment. This is further augmented by rupture of the liver in the fossa of the gallbladder. As to the location of these ruptures of the liver, Amante cites 320 cases, 103 of his own, 110 from Edler, 81 from Mayer, and 26 from Ogstonin,

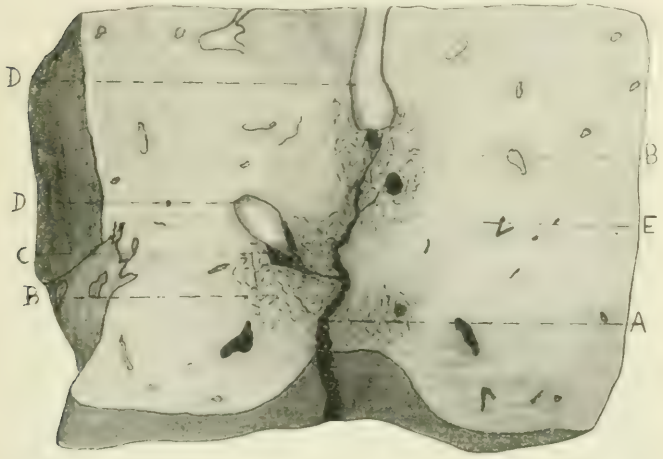

Fig. 2.—Sagittal section of the liver, showing the extent of the rupture into the liver substance from the fossa of the gallbladder. (*A*) rupture; (*B*) area of multiple small ruptures and slight softening; (*C*) periportal blood clots; (*D*) large branches of the portal vein; (*E*) normal liver.

in which the right lobe was injured in 212 cases, the left lobe in 60, and between the two lobes in 48.

Subcutaneous injuries of the liver may consist of (1) rupture of the capsule with the underlying parenchyma; (2) rupture of the parenchyma alone with hemorrhage into the space so formed, and (3) small multiple ruptures with the formation of multiple hematomas. This injury I have described is of the first type, the rupture of the capsule and parenchyma being continuous. This type may be very slight or consist of the entire avulsion of a lobe of the liver.

The mechanism of such ruptures of the liver is in general of three types; direct blows over the liver, produce injury at the point of contact; excessive bending of the liver with rupture of the superior or inferior surface; and indirect injuries (concussion) from sudden arrest of the liver after it has been propulsed in one direction, by means of the ligaments or by striking the backbone.

There are then two possible ways of explaining the cause of the injuries I have studied. First, by indirect force or concussion, which is borne out by the location of the external injuries about the head and shoulders. With the force of the blow applied to the head and shoulders, the liver would be thrown downward against the resistance of the abdominal viscera and the resistance offered by the suspensory and coronary ligaments, which would cause it to be bent in its anterior portions, resulting in rupture of the inferior surface. This would not, however, account for the simultaneous rupture of the adrenal and kidney. Second, by direct force, although the external injuries of the body do not reveal the location of any such blow; accompanied by bending of the liver. A blow applied to the costal margin, would transmit the force to the superior surface of the liver and cause it to be bent downward, the lateral borders being held more or less stationary by the ligaments. In this way the under surface of the liver would be subjected to a stretching force, and because of its limited elasticity, would tear. The wall of the gallbladder being under some tension from the fluid within and normally tougher, offered more resistance than the capsule of the liver, or the adhesions binding it to the liver. The bending and rupture of the under surface of the liver in the fossa of the gallbladder, tended to pull apart the capsule and wall of the gallbladder normally adherent; this force plus the direct force of the blow transmitted to the gallbladder was sufficient to detach it from the liver. That this latter explanation seems the more likely is supported by the extent of the detachment of the gallbladder, which corresponds exactly with the rupture of the liver. This explanation is further

strengthened by the simultaneous injury of the right adrenal and kidney in direct line with the tear of the liver; the force of the blow being transmitted to these organs through the liver and gallbladder.

March 11, 1918.

COMPARATIVE PATHOLOGY OF TESTICLE TUMORS

MAUD SLYE, HARRIET F. HOLMES
AND
H. GIDEON WELLS

Tumors of the testicle are common in horses and dogs, exhibiting quite the same characteristics as the corresponding tumors in man. They seem to be very rare in all other species, and no mention of such a tumor in the mouse can be found in the literature. In the Slye stock, among 19,000 mice dying natural deaths and examined postmortem, and about one half of which were males, twenty-eight instances of primary tumor of the testicle were found. Most of these resembled in all essential features the tumors that arise in the testicle of man and other animals, consisting of cells closely resembling the epithelium of the seminiferous tubules, arranged often in an alveolar structure. Despite great vascularity and a markedly atypical structure, no remote metastasis was observed, although in one case a series of six contiguous independent nodules was formed, and one case showed bilateral testicle tumors. Two of the cases seemed to be true spindle cell sarcoma, one arising at the site of a wound. Three of the typical "orchidoblastomas" also followed trauma. No evidence could be obtained that any of these tumors had arisen in a teratomatous growth, and no cases of teratoma have been observed.

One case of spindle cell sarcoma of the seminal vesicle of a mouse is described, apparently the second case of a tumor of this organ reported as occurring in a lower animal.

Two cases of primary spontaneous tumor of the testicle in dogs are described.

With the exception of one sarcoma, all the twenty-eight mouse testicle tumors occurred in the members of a single strain of mice and its hybrid derivatives, thus substantiating the statement that heredity influences the incidence of tumor development in different organs or tissues. This fact also probably explains the absence of any recorded cases of tumor of the testicle in mice from other laboratories.

April 8, 1918.

THE EFFECT OF THE ROENTGEN RAY AND THORIUM X ON TUBERCULOSIS IN THE GUINEA-PIG

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From the Laboratory of the City of Chicago, Municipal Tuberculosis Sanitarium

When this investigation was initiated it was determined to find a substitute for the roentgen ray in reducing the time necessary for making the diagnosis of tuberculosis in the guinea-pig. A roentgen-ray machine is not available to the average practicing physician, and it was thought that a chemical substance reputed to have a similar action to the roentgen ray would have a decided advantage. Among such substances might be mentioned benzol and thorium X. The experimental evidence on the value of the roentgen ray for increasing the susceptibility of guinea-pigs seemed to be fairly conclusive on superficial examination, but more critical consideration of these data revealed in some instances lack of proper controls and opportunity for false interpretation of results.

Murphy and Ellis,[1] on the basis of experiments reported by Lewis and Margot,[2] who noted that rats and mice experimentally infected with tuberculosis developed large spleens and that splenectomized ani-

1. Jour. Exper. Med., 1914, 20, p. 397.
2. Ibid., 1914, 19, p. 187.

mals lived longer after inoculation than normal animals, believed they saw a relationship between the lymphocyte and resistance to tuberculosis. They tested their ideas by infecting mice with bovine tubercle bacilli (1 mg.) and using as a criterion the duration of life, the roentgen-ray mice usually dying in about one third (7 and 9.7 days as compared to 18.5 and 23.3 days) the time required for the controls. As a result of their experiments, they conclude "Mice either normal or splenectomized after exposure to roentgen ray are markedly more susceptible to bovine tuberculosis than are normal animals."

Morton,[3] receiving his cue from the work of Murphy and Ellis, applied the roentgen ray to hastening the guinea-pig diagnosis for human tuberculosis. He found one massive exposure to the roentgen ray to reduce the total leukocytes from 12,000 to 15,000 cells per cm. by over one half (4,000 to 6,000), the reduction being mainly lymphocytes. The animals were radiated ten minutes with the Coolidge tube, the target being 12 inches distant from the base of the box containing the guinea-pig. A 5 milliampere current was passed through the tube, backing up 8½ inches of spark between points. Urine from ten cases of tuberculosis of the genito-urinary tract was used for infecting the guinea-pigs, and from this work Morton concludes that "In renal tuberculosis when it is necessary to resort to the use of animals, it ordinarily requires from five to seven weeks, while by the use of roentgen-rayed guinea-pigs the diagnosis can be made in from eight to ten days. The resistance can be sufficiently lowered by one massive dose of roentgen ray administered either shortly before or after the inoculation of the material to be tested."

Those of us who have been studying tuberculosis in guinea-pigs for years are inclined to lay greater emphasis on the rate of dissemination of the tuberculosis anatomically as a gauge of the virulence of the bacilli or the resistance of the animal rather than the duration of life as such an index, since death in tuberculosis is to so great an extent a question of accident.

3. Ibid., 1916, 24, p. 419.

The anatomic involvement was, therefore, used as a criterion of the effect of the roentgen ray and thorium X on the tuberculosis in the guinea-pig throughout these investigations. So that differences would be more striking very small doses of virulent human tubercle bacilli injected subcutaneously (from 0.000,001 to 0.000,000,1 mg. of a culture on Petroff's mediums in fine emulsion in salt solution) were used. Leukocyte counts were made every second day on the guinea-pigs, and in the final esperiments the leukopenia was used as a gauge of the effect of the roentgen ray and thorium X, keeping this as low as possible consistent with the life of the animal. In most cases in which exhaustive tests were made, a reduction of leukocytes (from 15,000 normal) to about 2,000 with oscillations was maintained for about one month.

Briefly, the following results were obtained:

A single exposure to the roentgen ray exactly as recommended by Morton, in spite of the fact that it causes a temporary drop in the circulating leukocytes, has practically no influence on the course of human tuberculosis in the guinea-pig as gauged by anatomic involvement.

Even a continued reduction in the circulating leukocytes (from 15,000 to approximately 2,000 to 4,000 per cm.) extending over a period of a month and existing at the time of infection, does not increase the susceptibility of the guinea-pig to human tubercle bacilli as gauged by the anatomic involvement with tuberculosis.

A single intraperitoneal injection of a solution of thorium X in physiologic salt solution sufficient to cause a reduction of the circulating leukocytes to about 1,500 per cm. for a short period of time, has practically no influence on the course of human tuberculosis in the guinea-pig; the maintenance of a leukopenia (as low as 2,000 to 4,000 leukocytes per cm.) for a period of a month likewise does not increase the susceptibility of the guinea-pig to virulent human tubercle bacilli as gauged by the anatomic involvement of the animal with tuberculosis.

April 8, 1918.

FURTHER STUDIES OF AN ANTI-POLIOMYELITIC SERUM

ITS PROTECTIVE AND CURATIVE PROPERTIES IN EXPERIMENTAL POLIOMYELITIS OF MONKEYS

JOHN W. NUZUM

It was first shown by the writer that repeated injections of the poliomyelitic coccus intravenously in animals produce antibodies in high titer, chiefly agglutinin, opsonins and complement fixation bodies. Furthermore, in a small series of experiments with monkeys, young rabbits and white mice, injections of immune sheep serum appeared to confer a limited degree of protection against fatal doses of recently isolated virulent poliomyelitic cocci. Still more recently, Nuzum and Willy have reported very favorable results in a series of 159 patients afflicted with infantile paralysis and treated with antipoliomyelitic horse serum in the Cook County Hospital during the summer and autumn months of 1917.

It appeared advisable to determine the question whether or not such a serum prepared by immunizing animals with the coccus of poliomyelitis possessed protective or curative properties for monkeys inoculated with fatal doses of highly virulent virus. A detailed study of the protective and curative properties of an antipoliomyelitic horse serum in experimental poliomyelitis in monkeys forms the basis of this paper.

SUMMARY

A highly potent immune serum can be produced in the horse by repeated intravenous injections of aerobic cultures of the poliomyelitic coccus.

Such a serum contains agglutinins, complement fixation bodies and especially opsonin in high titer.

Monkeys can be immunized against several fatal does of virulent monkey-adapted virus by repeated intravenous and intracerebral injections of the poliomyelitic coccus.

The serum of the horse immunized with strains of this coccus obtained from both human and monkey sources possesses both protective and curative properties against the virus in experimental poliomyelitis of monkeys.

For the paper in detail the reader is referred to the Journal of Infectious Diseases, 1918, 22, p. 258. Other studies in the etiology and serum treatment of poliomyelitis have appeared from time to time in various medical journals and for reference the reader is referred to the following articles:

Nuzum, J. W. and Herzog, Maximilian: Experimental Studies in the Etiology of Acute Epidemic Poliomyelitis, Jour. Am. Med. Assn., 1916, 67, p. 1205.

Nuzum, J. W.: Bacteriologic Findings in the Cerebrospinal Fluid in Poliomyelitis, Jour. Am. Med. Assn., 1916, 67, p. 1437.

Nuzum, J. W. and Willy, R. G.: Specific Serum Therapy of Epidemic Poliomyelitis; A Report of 159 Cases Treated with Antipoliomyelitic Serum, Jour. Am. Med. Assn., 1917, 59, p. 1247.

Nuzum, J. W.: The Protective Properties of Antipoliomyelitic Horse Serum (As Demonstrated by the Test of Amoss), Jour. Infect. Dis., in Press.

Nuzum, J. W.: A Study of the Neutralizing Properties of Antipoliomyelitis Serum (Neutralization of Virus in Vitro), Jour. Infect. Dis., in Press.

April 8, 1918.

PATENT DUCTUS ARTERIOSUS AND SACCULAR ANEURYSM OF THE AORTA

H. D. CAYLOR

From the Pathological Laboratory of Rush Medical College, Chicago

Mrs. C. was first seen in the summer of 1895 by Dr. Babcock. Her death occurred late in the autumn of 1917, twenty-one years after the first observation. When first seen she complained of disturbance of heart action, together with fear and coldness of the extremities. There was appreciable dyspnea on exertion but this did not incapacitate her. The first physical examination disclosed slight enlargement of the heart to the left with a very distinct presystolic thrill at the apex of the heart and a slight roughness of the first sound, scarcely a murmur. There was a marked machinery-like murmur in the left interspace close to the sternum. Although the bruit was continuous it had a crescendo and diminuendo intensity that did not agree with either systole or diastole. There was a thrill in this region and the two pulmonic sounds were audible. On these findings a diagnosis of patency of the ductus arteriosus was made together with some slight roughness of the mitral leaflets.

As years went on a dulness gradually appeared to the right

of the sternum with an increase in the second aortic sound. As this area of dulness increased the thrill and peculiar bruit at the left of the sternum diminished and finally disappeared and was replaced by a poorly-defined systolic murmur in the pulmonic area. The heart was gradually displaced to the left. At no time was there any cutaneous lesions of syphilis, and Mrs. C. had an apparently normal recovery from two operations, an appendectomy and tonsillectomy.

Necropsy.—The formalin-hardened heart with 15.2 cm. of the aorta, 9 cm. of the pulmonary artery, and 8.2 cm. of the superior vena cava weighs 485 gm. From the top of the middle of the left auricle to the apex of the heart the dimension is 15.4 cm. The greatest transverse dimension of the heart is 9.9 cm., at the auriculoventricular junction. The whole front of the heart is covered with yellow fat from 0.5-35 mm. thick, least noticeable opposite the middle of the right ventricle, most abundant opposite the junction of the right auricle and ventricle where it forms a thick yellow pad. There is less fat on the back than on the front of the heart, about two-thirds less. The apex of the heart is made up entirely of left ventricle.

There is a huge saccular dilatation of the first part of the aorta, 10.5 by 8 by 7.5 cm. in its greatest outside dimensions. The right, back, and front wall of the first part of the aorta is markedly thinned out to form the sac, so that in the body the aneurysm probably pointed to the right and downward toward the liver. The left wall of the first part of the aorta is apparently not involved in the dilatation. The innominate artery is also slightly dilated at its origin so that its diameter, measured from the outside, is 18 mm. The right auricle is compressed by this aortic dilatation so that it is 4.3 by 4 by 1.6 cm. in its greatest outside dimensions.

There is a band of fibrous adhesions 18 by 3 mm., infiltrated with yellow fat, between the front of the base of the aorta and the right auricle. There is a spontaneous rupture of the front of the aneurysm of the aorta, parallel to the pulmonary artery, 8 by 3 mm. Its lower end is 10 mm. from the base of the aorta; its upper end 15. The edges of the defect are ragged and there are dark brown shreds of fibrin here. From 6 to 8 mm. around the rupture, the wall of the aorta is stained dark brown with blood. A probe inserted through the slit goes into the aortic lumen.

About seven-eighths of the lining of the aorta is irregular from raised, yellow to white, firm, platelike thickenings that apparently extend through all the coats of the wall. The endothelium between the plates is slightly wrinkled. There is no lime here anywhere. The back end of the spontaneous

rupture of the aneurysm, already mentioned is 15 mm. above the origin of the right coronary artery and is 20 by 3 mm. The wall of the aorta is opaque, mottled with translucent patches, when it is held close to a light. The circumference of the aortic orifice is 9.5 cm., whereas that of the isthmus of the aorta is 7 cm. In a few places the endothelium of the aorta is absent and an irregular shallow ulcer remains. There is no clotted blood in the aneurysm anywhere; the saccular dilatation of the aorta easily contains the fist.

The left auricle is enlarged and is 10 by 6.3 by 2.3 cm. in its greatest outside dimensions. There is practically no fat beneath the epicardium of this auricle, whereas that of the right auricle is almost completely covered with yellow fat. The endocardium of the left auricle is smooth everywhere, and its wall is from 2 to 5 mm. thick. The circumference of the mitral ring is, with a little stretching, 9 cm. The endocardium of the back mitral leaflet is smooth. Some of the cordae tendineae of the back papillary muscles are fused. There are white, firm patches at the tendinous ends of some of the papillary muscles here. The thickening of the front mitral leaflet is nodular, most dense close up in the angle made by this part of the valve and the wall of the ventricle. This thickening is white, platelike, cartilage-hard and begins at the junction of the ventricle and valve and extends out from 6 to 13 mm.

The wall of the left ventricle is from 11 to 24 mm. thick. There are only two aortic leaflets, one on each side. The back leaflet is apparently absent. At the junction of the back and middle thirds of the right aortic cusp there is a raised, firm ridge, a suggestion of a connection of a back leaflet with the aortic ring. There are two corpora arantii in the right aortic cusp. The covering of the aortic cusps is very rough and irregular from thickenings similar to those of the front mitral leaflet. At the junction of the left aortic cusp with the ring there is a deposit of lime salts 3 mm. in diameter. The right coronary artery arises from two openings in this sinus of Valsalva. These immediately join to form the right coronary artery. The left coronary artery arises from one opening behind the left aortic cusp. The aneurysm of the aorta begins just above the aortic valve.

The lining of the superior vena cava is smooth as is that of the right auricle. The auricular muscles are firm cords here. The foramen ovale is closed by a thin membrane. There is no eustachian valve. The thebesian valve is a thin, threadlike strand of gray fibrous tissue 7 mm. long that stretches across the opening of the coronary sinus, bifurcating at its lower end and spreading out above into a thin,

semitransparent, gray, valvelike flap, 7 by 4 mm. The tricuspid ring, with a little stretching, is 9.5 cm. in circumference. The only change of the endocardium of the tricuspid valve is red-brown blood beneath the endocardium of the middle leaflet, in a region 1 by 2 mm.

The wall of the right ventricle is from 4 to 8 mm. thick. The covering of the pulmonary leaflets is grossly unaltered except of the left, where there is a yellow-white patch of thickening 8 by 6 mm. The pulmonary orifice is 5.3 cm. in circumference. In the lining of the pulmonary artery close to its bifurcation there are ten yellow to gray patches of thickening from 0.5-2 mm. in diameter. These all together are equal to about 1 sq. cm.

There is a patent ductus arteriosus 3.5 mm. in diameter, 10.5 cm. above the base of the pulmonary valve. The edge of this opening in the pulmonary artery is raised and firm, discolored brown. The wall of the pulmonary artery and aorta are intimately adherent here. The aortic end of the ductus arteriosus just distal to the isthmus, is 6 mm. in diameter. There is a marked thickening of the wall of the aorta opposite this. There are yellow to gray, flat thickenings of the lining of the pulmonary artery extending proximal from the opening in the pulmonary artery just described, toward the pulmonary orifice. These are equal altogether to about 1 sq. cm.

The lining of the coronary arteries is smooth throughout, as is that of the coronary sinus and its large branches. Large surfaces made by sectioning the myocardium are gray-brown and the yellow epicardial fat dips down into the muscles.

Microscopically, the wall of the aneurysm of the aorta is made up almost entirely of hyaline connective tissue fibers, interwoven with a few elastic bundles. At places the wall is abruptly broken across with the production of marked defects here. There is a marked infiltration of lymphocytes around the vasa vasorum of the aorta.

Anatomic Diagnosis.—Spontaneous rupture of a saccular aneurysm of the first part of the aorta; syphilis of the aorta; sclerosis of the front mitral and left pulmonary leaflets; slight sclerosis (syphilitic?) of the lining of the pulmonary artery; slight fatty infiltration of the myocardium; hypertrophy of the wall of the left ventricle, auricle and right ventricle; dilatation of the left auricle; petechial hemorrhage of the middle tricuspid leaflet; compressed right auricle; fibrous adhesions between the right auricle and base of the aorta; marked subepicardial fatty infiltration of the front of the heart; slight calcification of the left aortic cusp; patent ductus arteriosus; accessory opening of the right coronary artery.

May 13, 1918.

ON THE FORMATION OF CONGLUTINATED THROMBI IN THE LIVER OF THE DOG AFTER REPEATED INJECTIONS OF WITTE'S PEPTONE

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Dogs were given repeated intravenous injections of Witte's peptone. Doses of 1 gm. were followed by injections containing as much as 10 gm. of peptone. Changes in the liver were constant. In dogs dead of acute peptone poisoning, the microscopic appearance of the liver resembles very closely that of ordinary passive hyperemia. In those animals sacrificed after 8 and 15 days, there were found in the hepatic sinusoids solid plugs of more or less homogeneous material.

In the stages of the process studied, no changes were observed in the adjacent liver cells or endothelium. The thrombuslike masses are not believed to have been formed in the circulating blood and brought to the liver as occurs after the injection of a hemagglutinating serum. Injections of peptone cause a marked rise in blood pressure in the portal vein and also greatly increase the amount of lymph flowing from the thoracic duct. Most of this lymph has been shown to come from the liver. As a result of the obstruction to the outflow of blood from the liver and the loss of fluid from the blood in the liver, stasis occurs in the sinusoids and the red blood corpuscles become fused into masses (conglutinated), thus forming in situ the solid plugs described above.

May 13, 1918.

THE PRODUCTION OF PRECIPITINS BY THE FOWL

LUDVIG HEKTOEN

The domestic fowl is a prompt, reliable and liberal producer of precipitins, more so than the rabbit. A single intraperitoneal injection of 20 c. c. of defibrinated blood or serum in most cases in 10-12 days yields a precipitating serum of sufficient strength and specificity for practical purposes.

On account of an unwelcome tendency to give nonspecific reactions, especially on rapid transfer from low to higher temperatures, great care must be exercised in all tests with fowl antiserum, and 1.8 per cent. salt solution should be used in making all mixtures and dilutions.

May 13, 1918.

HEMOLYTIC STREPTOCOCCI ON THE BODY SURFACE

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In reviewing the literature, no work has been met with, giving experimental data on the subject of hemolytic streptococci in relation to the skin of the human body. Weaver obtained streptococci in small numbers from scales taken from the skin of the abdomen in a single case of scarlatina. He intimates that they probably had been transferred from the mouth to the skin. In this early work, differentiation into hemolytic and nonhemolytic was not determined. Raskin found streptococci on the scales 4 times in 20 observations, but never in the intact skin. Gordon's examinations of the skin for streptococcus were negative. Chipman recently remarks that "the streptococcus often, but by no means always, evinces a selective preference for

certain sites such as the folds of the skin, as in the axillary region." He neither refers to, nor offers experimental data to verify this statement.

Reference need only be made to standard textbooks on surgery and dermatology to ascertain the important etiologic rôle played by the hemolytic streptococcus in its relation to the skin. Erysipelas is of the greatest importance in this regard, the hemolytic streptococcus invading the skin, and being responsible for the production of this infection. Suffice it to merely mention also the importance of this organism in various surgical complications of war wounds, often leading to most serious results.

As a matter of prophylaxis, it is evidently of importance to know how commonly hemolytic streptococci are present on the skin of soldiers before the occurrence of wounds. Alexander has demonstrated that the hemolytic streptococcus is present in the dust, atmosphere, and floor sweepings of the quarters housing soldiers; there is, of course, the possibility of their presence in the soil, water, etc., and in the various vehicles and conveyances used to transport the soldiers to the evacuating stations and base hospitals, and also their presence on clothing.

In order to make a comparative survey of the surface of the body for hemolytic streptococci, a topographical outline was arranged corresponding much to the regiones corpores human of Spalteholz. This plan, therefore, included all of the exposed sites of the body surface, especial reference being given, however, to the head and hands, since these parts are practically always exposed. Cultures were taken with the ordinary platinum wire loop, first dipped in sterile water to insure adhesion between the organism and the loop. With a sterile scalpel the skin area was first scraped, in order that the deeper layers of the skin might be reached, and with a moderate amount of pressure the wire loop containing the sterile water was then applied. Cultures were made on blood-agar plates and then incubated for 24 hours at 37 C. Hemolytic streptococci, when present, grew typically as small, round, gray, raised colonies, with a wide,

clear zone of hemolysis around each colony. The suspicious streptococci appearing on the plates were then studied morphologically and culturally. Pathogenicity, sugar fermentations, and other properties were also determined, and will be detailed later.

In the first experiments, cultures were taken from 38 persons, all of whom, on inquiry, stated that they bathed at least once a week, and several said that they took shower baths every morning. The cultures were taken from the same areas on each body, in order to insure a comparative study. From this group, which may be called a "clean group," no hemolytic streptococcus colonies were isolated in any case. The organisms found were, as a rule, white staphylococci.

A second group, numbering 89 individuals selected largely from dispensary patients, and, as a rule, very filthy in their habits, were next examined in the same way as the first group. The results are as follows: From these 89 cases 15 strains of hemolytic streptococci were isolated from 8 different persons, thus giving 9 per cent. of the "filthy group" from which the organisms were isolated. Ten of the 15 strains of hemolytic streptococci were obtained from various regions of the head, 5 of which came from hairy parts. One colony was isolated from the tibia, which was thickly covered with hair. One colony was isolated from the hands. This gives 73 per cent. of the organisms isolated from the exposed parts of the body, the other organisms being obtained, as previously noted, from parts ordinarily covered by clothing.

Sugar reactions place these organisms on the basis of Holman's classification, into the group, "Streptococcus pyogenes." That is, they are hemolytic and ferment lactose and salicin, but not mannite.

Pathogenicity was determined by inoculating 2 c.c. of a 24-hour serum-broth culture into the ear vein of a rabbit. The weights of these animals decreased, the amount varying from 150-300 gm., and the temperature in each instance rose from 0.5-2.5 F. Arthritic joints developed in all of the rabbits, and on the 10th day when the animals were posted, pure cultures of

the streptococci, identical with those injected, were isolated from each of the swollen joints. One of the rabbits died on the 6th day, and showed a marked acute fibrinous pericarditis, pure cultures of the organism being obtained from the heart blood. Three of the rabbits showed little effect of the first injection, and required reinoculation on the 15th day. Subsequently they lost on the average 130 gm. in weight, and a rise in temperature of 1.5 F., and developed typical arthritic joints, from which hemolytic streptococci were isolated in pure culture.

To ascertain the probable duration of these strains on the skin, a loopful of a 24-hour serum-broth culture of a typical hemolytic streptococcus was rubbed into the skin with the wire loop at 3 points on the intact skin, and at 3 sites on the surface scraped with a sterile scalpel on the dorsum of the left hand. For a period of 34 hours the hand was not washed or wiped, and came in contact with clothing, only so far as was necessitated by their removal on retiring. Precisely the same experiments were performed at the same time on the right hand, which was washed with soap and water several times during the day. Cultures were taken each 10 minutes for the first hour, and each half hour for the succeeding 33 hours.

The colonies at but one site, on the right hand, survived the first washing, which was 4 hours after the experiment was inaugurated. This was on the scraped skin. One and one-half hours later, cultures from this area were negative.

On the left hand, two of the zones in the intact skin revealed colonies up to the 10th hour, the third site gave a positive culture a half hour longer. In the scraped skin, one area was negative at the 12th hour, the other two sites still giving positive results. At this hour, 8 p. m., I left the laboratory. At 8:05 a. m., the following morning, only one of the areas of the scraped skin yielded a culture of the organism. This site was negative at 10:30 a. m. These determinations were repeated on another occasion, and found, in the main, to be the same.

From the data collected in preparing this paper, no

colonies of hemolytic streptococci were isolated from the sites mentioned by Chipman, notwithstanding the fact that especial care and attention were given in making cultures from these zones.

Cultures taken from the finger nails were in all instances negative for hemolytic streptococci, but contained staphylococci and other bacteria.

From finding hemolytic streptococci in the series of cultures made by Malone and Rhea, and others from war wounds, it is easy to presume that in at least a certain percentage of cases, the hemolytic streptococcus is present as either a primary or a secondary invader, the organism being present on the skin previous to the occurrence of the wound, and starting mischief only when a better food medium presented itself.

SUMMARY

1. The data presented, indicates the prophylactic value of cleanliness on the streptococcus flora of the body surface.

2. In the "filthy group" composed of 89 cases, 9 per cent. revealed the presence of the hemolytic streptococcus on the skin of the body surface, whereas in the "clean group" of 38, not a single colony was isolated.

3. Of the 10 colonies isolated from the head, 5 were from hairy parts, the strain isolated from the tibia came from a region profusely covered with hair. This indicates that on the skin hemolytic streptococci incline more to the hairy parts than they do to the skin surfaces.

4. These streptococci isolated from the skin are distinctly pathogenic for rabbits, and behave in this animal quite like ordinary pathogenic hemolytic streptococci from other sources.

5. These streptococci appear to be typical hemolyzers, and on the basis of sugar reaction may be classed according to Holman, as "Streptococcus pyogenes." The name indicates their pyogenic character, they being the hemolytic streptococci commonly causing purulent infections.

May 13, 1918.

STREPTOCOCCI OF THE ACTINOMYCES-LIKE GRANULES OF THE TONSILS

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In 1914, Davis[1] called attention to the nature of the actinomyces-like masses that are commonly found in the crypts of the faucial tonsils.

The granules are grayish or yellowish bodies, rather firm in consistency and, on microscopic examination, have a raylike structure resembling sulphur granules of the actinomyces for which they have been mistaken. Their size is variable. They are usually small, about the size of a pinhead, but not infrequently are much larger. In one instance, a granule measured 15 mm. in all dimensions. They may be so small as to be visible only with the aid of a hand lens or a microscope. In the crypts of the tonsil, they lie free either near the base or near the orifice, through which they may protrude. They are quite brittle and when disintegrated have a foul and disagreeable odor.

The frequency of their occurrence is difficult to estimate. Careful examination of smears from crypts of almost all tonsils will reveal these masses in minute form. In the series examined by Davis these granules were visible to the naked eye in 30 of 122 pairs of tonsils. In the present series they were found in 31 of 135 pairs. If they are present, there is usually more than one.

In the present study, particular attention was directed to the streptococci found associated with the filamentous forms. In the smear preparations made from the crushed granules they appear in pairs, less often singly or in short chains. They intermingle freely in variable numbers with the bacilli and spirilla, and do not seem to have any characteristic distribu-

1. Jour. Infect. Dis., 1914, 14, p. 144.

tion. In some granules the cocci are very few in number, while in others they are the predominating organisms. They are strongly gram-positive.

For purposes of isolation of these cocci, the granules were collected from tonsils obtained immediately after tonsillectomy from patients, chiefly school-children from the ages of 5-16. The granule was first washed several times in sterile salt solution and then crushed by a sterile knife. Plain agar with a reaction of 1 +, to which defibrinated human blood was added in the proportion of 1 : 20, was inoculated with a loopful of material, and then poured into petri dishes. Three dilutions were made. The plates were then incubated under both aerobic and anaerobic conditions. To remove the oxygen, the alkaline pyrogallic acid mixture was placed in the bottom of the desiccating jar. The plates were placed above, and the jar was firmly sealed to exclude air. The anaerobic plates were incubated for 48 hours.

SUMMARY

The results of a study of streptococci from the granules, using the above mentioned technic, are summarized as follows:

Two types of streptococci, the hemolytic and the viridans, were isolated from the actinomyces-like granules of the tonsils.

The viridans type showed strong anaerobic properties. The hemolytic cocci did not.

Otherwise, the streptococci, in their cultural and morphologic characteristics and pathogenic properties, resemble streptococci from various parts of the mouth and from the crypts of normal and diseased tonsils.

According to the classification of Holman, the hemolytic organisms isolated from the granules are of two varieties; (1) the Streptococcus pyogenes, and (2) the Streptococcus anginosus. The viridans types also are of two varieties; (1) the Streptococcus mitis, and (2) the Streptococcus salivarius.

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TRINITROTOLUENE IN RABBITS

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Following the extensive use of trinitrotoluene as a shell filler in the manufacture of munitions, many cases of poisoning among those working with it have been reported. Hamilton[1] states that, in 1916, 703 cases with 13 deaths were reported in America. The poisoning takes the form of a gastritis, both mild and very severe, toxic jaundice, or anemia of the aplastic type with or without jaundice. The prognosis in cases with jaundice and anemia is very doubtful. It was thought from these symptoms that, as with some other benzene derivatives, the poisoning is due in part at least to a destruction of the blood elements and a liberation from them of toxic products, and it was hoped that a careful study of the blood might aid in the diagnosis of incipient poisoning. Pure benzol itself is a powerful leukotoxin and, as Selling[2] has shown, in rabbits it destroys the myeloblastic tissue of the marrow almost completely. Dinitrobenzene, which is used less extensively than T N T in the making of explosives, has been shown by Malden[3] to reduce the number of red cells, produce varieties in size and shape, basophil granulations and occasional nucleated reds. The total white count is increased but with a relative decrease in the polymorphonuclear leukocytes, the eosinophils sometimes and the mast cells more often being relatively and absolutely increased. Anilin, which is produced from benzene by the replacement of one of the H atoms by a NH_2 group, acts chiefly on the red cells, reducing their number and causing variations in size, metachromasia, occasional nucleated red cells and basophil granulations. The studies so far of the blood of those exposed to the dust and fumes of T N T have revealed

1. Med. and Surg., 1917, 1, p. 761.
2. Johns Hopkins Hosp. Rep., 1916, 17, p. 83.
3. Jour. Hyg., 1907, 7, p. 672.

very little. Panton[4] in England examined the blood of 50 women working in a T N T factory and found no anemia and no morphologic changes in the cells. The leukocytes were slightly increased in number with a relative increase in the polymorphonuclears, the eosinophils in a large number of cases being also increased. More recently Smith[5] in America studied the blood of 25 men working in a room in which the air was more or less constantly filled with the dust of T N T. His results agree with Panton's.

My experiments with rabbits were made with a view to determine the chief portal of entry of the poison, what early changes occur in the blood if any, and the effect on the various organs including the bone marrow. Three sets of 4 animals each were treated as follows: in one set, large areas of the skin were shaved on both sides of the animal and T N T soaked in olive oil was rubbed in vigorously every day for a week. The olive oil, it was thought, would aid in absorption as it has been found that there occurs more cases of poisoning among men with greasy hands. The second set was placed for an hour every other day for 10 days in a glass covered box into which through a hole in the bottom an inverted funnel conducted the fumes of T N T, which was heated in a crucible to 200 C. The flare of the funnel fitted over the crucible and the stem went through the hole in the box. This was carried out under a hood; nevertheless in the room outside, even with the window open, the fumes were strong enough to cause a bitter taste and produce a slight headache. In a third set the T N T was weighed, placed in gelatin capsules, and pushed down the throat. In the first two sets of experiments the results were entirely negative. After the rabbits had been exposed to the fumes for a short time they would sneeze and rub their nose, and appear very drowsy. In neither set were there any other symptoms. The blood was not appreciably affected. The total and differential counts were normal, and there were no morphologic changes. The animals were killed at the end of the experiments

4. Lancet, 1917, 2, p. 77.
5. Jour. Am. Med. Assn., 1918, 70, p. 231.

and sections made of the liver, kidney, spleen and marrow of the femur. In some the liver showed very slight fatty changes and the kidney showed areas of very slight inflammation with a beginning round-cell infiltration. But these changes were not more marked than in an equal number of supposedly normal rabbits. It is possible that these experiments were not carried on for a sufficient length of time, and that the absorption was too slight to produce any changes.

The feeding experiments were more interesting and should be carried further. One rabbit received 1 gm. on 2 successive days and died the 3rd day; another received the same dose and died the 4th day; another received only 0.25 gm. and died the 3rd day, while a fourth began with 0.25 gm., 5 days elapsed before the second dose of 0.25 gm. was given, and then the dose was increased to 0.5 gm. and repeated every other day until the animal had received 9 gm. when it became very ill and was killed. These results suggest great individual variation in susceptibility. The blood examination in these animals revealed a slight reduction in the red cell count, there being a loss of about 1 million after 0.25 gm. but not more even after 9 gm. There was no change in the white cell count. There was very little morphologic change, no poikilocytosis, basophil granulations, nor nucleated red cells. There was some anisocytosis, the larger type of cell predominating. While making the white cell counts, numerous small refractile bodies were observed, which on staining lightly with carbol thionin appeared as light blue round bodies, being apparently in process of extrusion from the red cells. They were about twice the size of a platelet and many were free. Careful staining with the Jenner, Wright and Giemsa stains did not bring them out; fixation in formalin and staining in hematoxylin brought them out in fairly deep lavender color. Whether they were degenerating or imperfectly formed nuclei or something quite different I do not know. The 4 animals all showed a relative increase in the polymorphonuclear leukocytes but no increase in the eosinophils such as Panton and Smith found in their patients. At necropsy the urine was

dark brown. The test for bile was negative. After 9 gm., albumin and casts were found but no blood. The spleen was very nearly black, but the other organs were normal. The microscopic study of the liver and kidney showed no changes. The spleen was filled with blood and pigment, and the marrow of the femur showed a slight increase in the red forming cells.

CONCLUSIONS

1. Rabbits are not poisoned by small doses of T N T rubbed into the skin nor by exposure to the fumes of T N T for a short length of time.

2. There is great difference in individual susceptibility to doses taken by mouth, and the only appreciable changes in the blood are a slight reduction of the red cells, a relative increase in the polymorphonuclear leukocytes, and the appearance of round bodies in the red cells which with special fixation take a nuclear stain lightly. The only demonstrable changes in the organs are an increase of pigment in the spleen and a possible increase of the red forming cells of the marrow.

May 13, 1918.

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